MEMORANDUM

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TO Karen Weiss, M.D., Director, Division of Clinical Trial Design and Analysis, Office of Therapeutics Research and Review, CBER.

TOPIC Final Clinical Review
Biologic License Application STN BL 125036/0 for alefacept for treatment of moderate to severe chronic plaque psoriasis

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I. INTRODUCTION

Filing of License Application

On August 6, 2001 Biogen submitted to the Center for Biologics Evaluation and Research a Biologics License Application (STN BL 125036/0) for alefacept for the treatment of psoriasis.

Drug Product

Alefacept (LFA3TIP) is a recombinant glycosylated fusion protein consisting of the first domain of human LFA3 fused to the hinge and constant regions (C_H2 and C_H3) of a human IgG1 heavy chain. The protein is expressed by Chinese hamster ovary cells and is secreted as a 91.4 kD, disulfide-linked dimer.

The drug product is a sterile lyophilized powder containing LFA3/IgG1 10 mg/ml per vial and various excipients. The product is stored at room temperature and is reconstituted with water. In the clinical trials placebo consisted of 0.9% Na Cl.

Rationale and Hypothesis

LFA-3 is a CD2 receptor ligand and enhances adhesiveness of T lymphocytes to antigen-presenting cells. CD2/LFA-3 interactions transduce signals not only to T lymphocytes but also to interacting monocytes resulting in secretion of cytokines involved in T lymphocyte responses. The immune response starts with interaction of T lymphocytes with antigen presenting cells. The binding of co-stimulatory molecules with their ligands (e.g. CD2/LFA-3, LFA-1/ICAM-1, CD28/B7, CD4/class II, and CD8/class I) is required for optimal T lymphocyte activation. Inhibiting the co-stimulatory interactions may reduce T lymphocyte responses. CD2 is expressed on all subsets of T lymphocytes and natural killer cells. CD2 increases T lymphocyte responses initiated through the T cell receptor (TCR/CD3). CD2 binding to LFA-3, co-stimulates T lymphocyte proliferation and cytotoxic T lymphocyte and NK effector functions.

Activated T lymphocytes may play a role in autoimmune diseases including plaque-type psoriasis and interference with T lymphocyte activation may be therapeutic. Blocking or reducing T lymphocyte activation may improve the clinical manifestations of psoriasis.

Proposed Indication: Plaque Psoriasis

Psoriasis is a chronic skin disorder characterized by erythematous, scaly papules and plaques with a predisposition for the scalp, extensors of the limbs, lumbosacral area and genitalia. The condition affects between 1 and 3% of the general population. However, it is relatively infrequent among African-Americans, in Japanese populations and in the Native American population. Men and women are equally affected.

Psoriasis has a bimodal peak of onset, one in adolescents and young adults (at 16 to 22 years of age) and the second in older persons (at age 57-60). Onset is before the age of 15 in 27% of cases. Early onset disease is strongly linked to HLA Cw6 and DR7, while late onset disease is linked to HLA-Cw2. The predisposition to psoriasis is thought to be

polygenic with expression triggered by environmental factors such as streptococcal infection, stress, certain drugs, and HIV. The cause of psoriasis is not fully known.

Psoriasis is characterized by excessive proliferation of keratinocytes and inflammation. There is evidence that activated T cells are involved in the pathogenesis of psoriasis. In addition, abnormalities in cytokine expression, intracellular signaling, and polyamine metabolism may mediate psoriasis.

Plaque psoriasis is the most common form. The lesions are indurated/raised, erythematous and scaly. Approximately 1/3 of patients have moderate to severe disease. The disease waxes and wanes. Spontaneous remissions and relapses are the rule. Spontaneous durable remissions may occur.

Guttate (drop-like) psoriasis is sometimes triggered by streptococcal infection and is associated with development of chronic psoriasis. Pustular psoriasis varies in severity from localized to generalized forms with fever, malaise, and a relatively high mortality after prolonged courses. Erythroderma can be complicated by sepsis, temperature instability and high output cardiac failure. Psoriatic arthritis is a complication in approximately 10% of all psoriasis patients.

Patients with psoriasis report reduction in mental and physical functioning comparable to that seen in patients with cancer, or arthritis, The chief complaints of patients with psoriasis are scaling, itching, redness and tightness of the skin, bleeding and burning sensations. In a 1998 National Psoriasis Foundation Patient-Membership survey, patients reported depression, difficulties in the workplace and socialization caused by psoriasis.

The goal of treatment of psoriasis is to decrease the severity and extent of psoriasis to the point that it no longer interferes with the patient's occupation, personal or social life, or well-being.

Licensed Therapies for Psoriasis

Topical Therapy:

The initial treatment of stable plaque psoriasis affecting less than 10-20% of body surface area is topical. Topical therapies include emollients, corticosteroids, anthralin, tar, retinoids, calcipotriene, and salicylic acid. The mainstay of treatment is topical corticosteroids. Topical corticosteroids induce skin atrophy striae, purpura and may be absorbed systemically leading to suppression of the hypothalamic-pituitary-adrenal axis. Another possible limiting factor to their use is tachyphylaxis. Other commonly used topical agents include calcipotriene (a vitamin D analogue), tazarotine (a retinoid prodrug) and anthralin. Salicylic acid is used as a keratolytic agent. Skin irritation is the most common adverse effect of these topical agents.

Phototherapy:

Phototherapy for psoriasis includes UVB, narrow band UVB, and psoralen, a photosensitizer, plus UVA (PUVA). PUVA induces responses in a high proportion of patients and can induce long-term remissions. PUVA causes premature aging of skin and

increases the risk of cutaneous malignancy in a dose-related fashion. The relative increase in risk of a person with sun-sensitive skin (e.g. Fitzpatrick Type I or II skin; always burn; tan never/sometime) developing squamous cell carcinoma is at least 5 times greater than that of control.

Systemic Therapy:
These products in general induce moderate improvement (≥75% clearing) in the majority of treated patients. These products are recommended for severe and/or recalcitrant psoriasis because they induce serious toxicities. Methotrexate, an antimetabolite folate analogue, appears to be more active in the treatment of psoriatic arthritis and pustular psoriasis than plaque psoriasis. Methotrexate may cause leukopenia, dose-dependent development of cirrhosis of the liver and severe pneumonitis. Methotrexate is also fetotoxic and an abortifacient. Cyclosporine, an immunosuppressant calcineurin inhibitor, induces hypertension, kidney disease, increased risk of malignancy (especially B cell lymphoma) and infection. Retinoids are the treatment of choice for pustular psoriasis and have also been used in the treatment of erythrodermic psoriasis. Of major consideration in women of childbearing potential is teratogenicity of retinoids. Other serious adverse events are hepatotoxicity, pancreatitis, depression, visual impairment, and hyper-triglyceridemia.

Immunosuppressive Agents and Anti-metabolites: Risk/benefit in Psoriasis:
Psoriasis is a serious chronic disease associated with significant morbidity and impairment. The disease is usually not life threatening and does not induce irreversible injury to skin or other organs, with the exception of psoriatic arthritis. A number of serious toxicities are associated with the use of immunosuppressants and antimetabolites. These include serious infections, and neoplasms. In the case of neoplasms there may be a lag in the time to clinical detection and long-term follow-up of treated patients may be required to assess the excess risk. Therapies associated with significant risk of serious irreversible toxicity or mortality should be reserved for patients with severe, recalcitrant psoriasis. Long-term continuous treatment is usually not recommended. The goal of therapy is to bring disease under control and change to the least toxic therapy.

Licensing Status of Drug Product
At the time this application was submitted, alefacept was not licensed in any country, nor had it been withdrawn from the market in any country.

Disclosure of Financial Interests and Arrangements of Clinical Investigators
Dr. Gerald Krueger who participated as a clinical investigator in studies C97-708, C98-709, C99-711 and C99-714 has disclosed significant payment of other sorts from Biogen made on or after February 2, 1999 in the amount of ---------- for consulting fees and expenses and for an Investigator Run Trial Grant Payment.

Debarment Certification

Biogen has provided certification that it did not and will not use the services of anyone debarred under Subsections A or B of Section 306 of the Food, Drug and Cosmetics Act in connection with this application.

II. PHASE 1 STUDIES

PK Studies in Normal Subjects

Table 1 lists three single-center non-IND phase 1 studies conducted to assess the pharmacokinetics of alefacept in subjects not affected by psoriasis.

Table 1. Non-IND Phase 1 Studies in Healthy Subjects

Study #	Design (N)	Dosing
C95-701	Placebo- controlled single-dose, dose-escalation. N= 42	0, 0.005, 0.01, 0.02, 0.04, 0.1, 0.15, 0.225 mg/kg IV
C96-704	Open-label randomized, parallel group, single-dose. N=16	0.04 mg/kg IM or IV
C97-706	Double-blinded, placebo-controlled, randomized, single-dose study. N=54. -Part 1: Dose-escalation of BG9712. -Part 2: Parallel-group comparison of BG9712 and BG9273.	BG9712: IV infusion of 0.04 mg/kg, IV bolus of 0.04 mg/kg, IV bolus of 0.15 mg/kg, ? IM injection of 0.15 mg/kg, SC injection of 0.15 mg/kg, BG9273: IV bolus 0.15 mg/kg

PROTOCOL C95-701

Study Design

A phase 1, intravenous single-dose, controlled, blinded, dose escalation study was carried out in healthy volunteers in the UK. Seven cohorts of six subjects each were enrolled. Four subjects in each cohort received BG9273 and two subjects received placebo. The doses were 0.005, 0.01, 0.02, 0.04, 0.1, 0.15, and 0.225 mg/kg. A return to normal range of absolute lymphocyte counts was required in all subjects within a dose group before dose escalation. The study evaluated tolerability, pharmacokinetics and biologic activity (lymphocyte counts, delayed hypersensitivity testing).

Results and Discussion

Pharmacokinetics:

No data are available from the 0.225 mg/kg dose group. The disposition of BG9273 appears linear with peak serum concentrations ranging from 0.3 µg/ml to 2.74 µg/ml. The serum clearance was 0.3 ml/h/kg. The terminal serum half-life was approximately 200 hrs and the distribution volume ranged from 70-90 ml/kg.

Adverse Events:

No serious adverse events were reported. The investigator brochure cites episodes of myalgias with headaches (two), chills (one), arthralgias (one) and morbilliform rash considered likely related to BG9273. No severe adverse events were reported. There were

no differences in the reported adverse events between the BG9273-treated groups and the control group (except for decreased lymphocyte counts, see below).

Clinically Significant Laboratory Abnormalities. Lymphopenia:
No subject who received 0.005 mg/kg had a reduction in peripheral lymphocyte count. In the 0.01 mg/kg cohort two subjects developed lymphopenia (attributed to viral illness) that resolved within seven days. In the 0.1 and 0.15 mg/kg cohorts all BG9273 treated subjects had decreases in lymphocyte counts beginning at 4 hrs after infusion of drug with return to baseline by 48 hours. The decreased count was due to decreases in CD2+ cells, namely CD4+ and CD8+ lymphocytes. In the 0.225 mg/kg cohort all four BG9273 treated subjects had decreased lymphocyte counts that returned to normal by four days in three of the four subjects. One subject had persistently lower than normal counts (5-15%) until day 35. The degree of reduction in lymphocyte counts correlated directly with the dose of BG9273. No changes in B lymphocytes (CD19+) were observed. The mechanism of these changes is thought to be cytolysis of lymphocytes

Reviewers' comments
Total lymphocyte counts appear to be lowered at all dose levels and range from about 85% to 45% of baseline at 4 hrs after the infusion. CD4+ counts are lowered by the same amount as total lymphocyte counts; the magnitude of CD8+ decreases appears to be greater than that of CD4+ (range 70% to 30% of baseline). Circulating B lymphocyte counts appear unaffected. The lymphopenia is possibly an extension of drug's the mechanism of action.

Decreases in Staining Intensity of CD2+ Lymphocytes:
The sponsor states that at doses greater than 0.02 mg/kg, decreased CD2+ staining intensity was observed in all subjects. The decrease is called transient. The degree and duration of reduction of staining correlated with dose of BG9273. There was no change in CD4+ or CD8+ staining. The decrease in CD2+ staining could be due to interference by BG9273 with the anti-CD2+ antibody used in the assay, removal from circulation of cells expressing high density of CD2+, or down-modulation of CD2+ from cell surface of lymphocytes.

Reviewers' comments
A decrease in mean CD2+ staining intensity of CD4+ lymphocytes is seen at all dose levels. For the 0.225 mg/kg dose level the decrease in staining intensity is persistent (percent intensity is about 70% of baseline at the final sampling time). Findings for CD8+ lymphocytes are similar. At levels > 0.1mg/kg complete recovery of CD2+ staining intensity may not have been reached. The clinical significance of a decrease in the mean CD2+ staining intensity of CD4+ lymphocytes is not known.

Neutrophil Elevations:
The absolute number of neutrophils increased up to five-fold in all subjects who received BG9273. The rise occurred within four hours of dosing and returned to normal by 24 hrs.

The magnitude or duration did not appear to be related to dose. There were no clinical findings associated with the elevations in neutrophil counts.

PROTOCOL C96-704

Study Title

"Tolerability, pharmacokinetics, and biologic activity of BG9273 (LFA-3/IgG, fusion protein) when given as an intravenous infusion or as an intramuscular injection: an open-label, randomized, parallel group study in healthy male volunteers"

Study Objectives

To compare the pharmacokinetics and tolerability of a single 0.04 mg/kg BG9273 dose when administered as an IM injection or as a 30 minute IV infusion. To determine the pharmacokinetics of a single 0.04 mg/kg BG9273 dose when administered as an IM injection or as a 30-minute IV infusion.

Study Design

Phase 1, open-label, randomized, parallel group study in healthy men. Eight (8) subjects received 0.04 mg/kg BG9273 by 30-minute IV infusion, 8 subjects received 0.04 mg/kg BG9273 by IM injection.

Clinical and Laboratory Assessments

Adverse event reporting, physical examination, vital signs, ECG monitoring, hematology, peripheral lymphocyte subsets, immunoglobulins, serum C3 and C4 complement, blood chemistry, urinalysis, assessment of the injection site, subject assessment of injection site pain. Blood drawn for determination of antibody formation to BG9273.

Results and Discussion

Sixteen (16) Caucasian men ages 23 to 38 years were enrolled; 15 completed, 1 lost to follow-up,16 analyzed. Peak serum BG9273 concentrations following IM injection were approximately 30% of the peak concentrations achieved following IV infusion. Serum BG9273 concentrations became observable approximately 6 hours following IM injection and peaked approximately 3 days following injection. Absorption phase was complete between 4 to 6 days.

The relative bioavailability of IM injection to IV infusion based on AUC was about 50%. This apparent incomplete absorption may be due to limited assay sensitivity (0.075 µg/ml) or pre-systemic clearance by the lymphatic system. Following absorption, BG9273 appeared to be eliminated from serum at a rate consistent with the IV half-life. The elimination half-life following IM injection was nearly 10-fold longer than the absorption half-life. Mean serum pharmacokinetic parameters are shown in **Table 2.**

Table 2. Pharmacokinetic parameters

	IV Infusion	IM Injection
C_{max} (µg/ml)	0.96	0.29
T_{max} (h)	2.8	78
AUC (µg.h/ml)	197	105
$T_{1/2}$ Absorption (h)	-----	26
$T_{1/2}$ Elimination (h)	254	165

The most common adverse events were headache (19%), pharyngitis (19%), rash (19%), and myalgia (13%). No serious events were reported. At the injection site following IM injection, 4 subjects (50%) had mild erythema and induration, 2 (25%) had tenderness and mild pain, and 2 subjects (25%) developed palpable, but non-tender, lymph nodes. Erythema and induration was 3 mm or less. No clinically significant abnormalities were noted during physical examinations, vital signs, or ECGs. No antibodies to BG9273 were detected.

There were transient increases in neutrophil count following IV infusion and IM injection. Total lymphocyte count, CD2, CD3, CD4, CD8, and CD19 counts decreased in more subjects within 24 hours of IV infusion than after IM injection. No subject's lymphocyte count was below the lower limit of normal. The following abnormal laboratory values were observed: Elevated CK (3X upper limit of normal 13 weeks after dosing) with CK-MB just above upper limit of normal; positive urobilinogen (one subject), proteinuria (4 subjects), hematuria (two subjects).

Reviewers' comments
The administration of drug IM induced localized reactions that were tolerable. Systemic absorption of drug by IM route is substantially lower and has a different PK profile. This may reflect increased exposure and clearance of alefacept by the lymphatic system. A number of clinically significant abnormal laboratory values were observed (clinical chemistry, urinalysis). The etiology of these is unclear. No significant changes in T cells were seen at the doses tested.

PROTOCOL C97-706
Study Title
A Randomized, Placebo-Controlled, Single-Dose Study in Healthy Male Volunteers of BG9712 and BG9273[1].

Enrollment Criteria
Inclusion criteria: Healthy men, ages18-45, who were within 15% of body mass index.

[1] BG9712 is an alefacept drug product that was dropped from development due to lower pharmacodynamic and clinical activity when compared to BG9273, the alefacept drug product used in the efficacy trials.

Exclusion criteria: evidence of viral or bacterial infection, history of severe allergic or anaphylactic reactions; history of significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, dermatologic, psychiatric, renal and/or other major disease; prior treatment with an immunosuppressant or an antibody.

Clinical and Laboratory Assessments

History and physical examination, VS, chemistry, hematology, lymphocyte subsets, urinalysis, ECG, immunoglobulins, complement, adverse events, anti-alefacept antibodies, alefacept concentrations,

Results

Pharmacokinetics: For the 0.04 mg/kg BG9712 dose the Cmax was comparable by IV infusion or as a bolus, AUC was somewhat reduced in subjects receiving the bolus. Bioavailability followed the pattern: IV>IM>>SC. For the 0.15 mg/kg BG9712 dose, the SC route yielded mean Cmax and AUC values 20% and 35% of those values obtained by IV bolus. The IM route yielded mean Cmax and AUC values 30% and 75% of those values obtained by IV bolus. Elimination half-life appeared unaffected by the route of administration. BG9712 yielded somewhat lower concentration of alefacept (83%) compared to BG9273.

Safety: No serious adverse events were reported. There was no suggestion of cytokine release or capillary leak syndrome. A greater number of subjects had greater decreases in lymphocyte subsets after dosing with BG9273 than after BG9712. No significant reductions in serum C3 and C4 and immunoglobulin. No antibodies to alefacept. When compared with the control group, subjects receiving 0.15 mg/kg alefacept IV experienced transient lymphocytopenia, the effect appeared more marked for BG9273. Minor depression of lymphocyte and subsets was observed for the IM dose of 0.15 mg/kg consistent with reduced concentrations of alefacept by this route. Two thirds of subjects had transient elevations in neutrophil counts.

Phase 1 Studies of Alefacept in Patients with Psoriasis

Table 3 lists the Phase 1 clinical studies conducted in patients with psoriasis. These studies are reviewed primarily from the perspective of clinical safety and activity of alefacept. Included in this listing are two studies of BG9712, an alefacept drug product that was not developed further because of lower PD and clinical activity compared to BG9273.

PROTOCOL C96-703

Study Title

"A randomized double-blind, repeat-dose, dose escalation study to evaluate the tolerability, pharmacokinetics, biologic activity and efficacy of BG9273 (LFA-3/IgG1 fusion protein) in patients with chronic psoriasis."

Study Objectives

Evaluate the safety, pharmacokinetics, effect on delayed-type hypersensitivity, and activity of eight once weekly doses of BG9273.

Table 3. Phase 1 Safety, Activity, and PK/PD Studies Reported in the Original Submission

Study Title	Design (N)	Dosing	Objectives
C96-703: Randomized, double-blind, dose-escalation study to evaluate tolerability, pharmacokinetics, activity, and efficacy of alefacept given once weekly for eight doses in subjects with chronic psoriasis.	Blinded, randomized, dose-escalation. N=33	BG9273 0.005-0.075 mg/kg IV weekly; 0.05 mg/kg IM weekly x 8 weeks	Safety, PK, activity, DTH of alefacept
C96-705: Randomized, double-blind, dose-escalation study to evaluate the tolerability, pharmacokinetics, activity, and efficacy of alefacept given once every 4 weeks for two doses in subjects with chronic psoriasis.	Blinded, randomized, dose-escalation. N=19	BG9273 0.05, 0.10, 0.15 mg/kg monthly IV x 2 months	Safety, PK, activity, DTH of alefacept
C98-709: Randomized, multiple-dose, dose-escalation study of tolerability and plasma concentration of alefacept in subjects with moderate to severe plaque psoriasis	Blinded (to dose), randomized, dose escalation. N=123	BG9712 0.15-0.75 mg/kg weekly IV, IM, SC x 12 weeks	Safety, activity, PK/PD
C98-710: Blinded, multiple-dose, study to determine tolerability of repeated courses of Alefacept in subjects with moderate, moderate to severe and severe plaque psoriasis	Open label (after C97-708 data lock) retreatment. N=141	BG9712 0.0125-0.15mg/kg weekly IV x 12 weeks	Safety of repeat courses of alefacept
C99-716: Single center, multiple-dose, open-label study of the effect of alefacept on psoriatic lesional Tcells in situ in subjects with chronic plaque psoriasis	Open label. N=9	BG 9273 7.5 mg weekly IV x 12 weeks	PD, effect of alefacept on lesional T cells in situ
C99-718: Randomized, open-label, controlled study of the effect of intravenous alefacept on T cell dependent humoral responses to recall and neoantigens in patients with chronic plaque psoriasis	Open label, randomized. N=46	BG9273 7.5 mg weekly IV x 12 weeks	PD: T cell humoral response to neoantigen and recall antigen

Study Design

This was an uncontrolled, multicenter, multiple-dose, dose-escalation study of BG9273 administered intravenously once weekly for eight weeks in 18 subjects with moderate to severe chronic psoriasis. In the original protocol three doses 0.025, 0.05, and 0.075 mg/kg were planned. In the first cohort four subjects would receive 0.025 mg/kg open-label. In the subsequent second and third cohorts treatment assignment was randomized and double-blinded. In the second cohort, two subjects would receive 0.025 mg/kg and four subjects would receive 0.05 mg/kg. In the third cohort, two subjects would receive 0.05 mg/kg and six subjects would receive 0.075 mg/kg.

Reviewers' Comments

The protocol was modified to add a dose cohort of 0.005 mg/kg. This starting dose was expected to produce measurable blood levels of drug and some pharmacodynamic effects; in addition, the dose would expand the range of the maximal drug concentrations achieved at steady state thus increasing the pharmacokinetic exposure from a three-fold to a ten-fold range. An IM dose cohort (0.05 mg/kg) was also added. The investigators were given the option of administering the IV dose as a bolus or as an infusion.

Standard Treatment

The use of mild to moderately potent topical corticosteroids was allowed.

Multiple Dosing Rules

Each dose was separated by an interval of at least seven days. The absolute lymphocyte count was to be ≥ 75% of the lower limit of normal within 24 hrs before dosing. From the pre-dosing sample from the previous dose, the absolute number of any of the lymphocyte subsets CD4+, CD8+, or CD19+ must be ≥ 75% of the lower limit of normal.

Dose Escalation Rules

Progression to next dose group would occur after the last subject in the previous dose group received the fourth dose of study drug and safety data including hematology, chemistry, urinalysis, and adverse events were reviewed. Progression to the next dose would not occur if a subject experienced a reduction in absolute number of lymphocytes or lymphocyte subsets (CD4+, CD8+, or CD19+) that met all the following criteria: related to study treatment, <50% of lower limit of normal, ≥ 50% reduction from baseline, sustained > 28 days post-dosing in any two consecutive determinations made after the 28th day.

Withdrawal Rules

Permanent discontinuation was required for: pregnancy, subject's wishes, investigator or sponsor's discretion. Patients who withdrew because of non-safety reasons could be replaced.

Inclusion Criteria

Men or women between the ages of 21 and 70 years with: moderate-to-severe chronic plaque-type psoriasis with body surface area involvement ≥ 10%; body weight within 50% of ideal; normal ECG; lack of clinically meaningful abnormalities in CBC and

differential count, serum creatinine, LFTs; stable dose (at least 14 days) of maintenance medication.

The sponsor was asked to specify what baseline level of total lymphocyte count and CD4+, CD8+ counts are acceptable and to require a history of systemic treatment or phototherapy as an entry criterion; subjects controlled with topical therapy alone would not be studied.

Exclusion Criteria

Erythrodermic, guttate, or palmar pustular psoriasis. Unwillingness to practice adequate contraception. History of severe allergic or anaphylactic reactions. History of clinically significant disease. Serious local or systemic infection within previous three months. Fever or symptomatic viral or bacterial infection within one week of the first dose of study drug. HCV, HBV, HIV infection. Treatment with systemic retinoids or systemic immunosuppressant (e.g. high dose steroids, >25 mg prednisone/day) within four weeks. UV therapy within two weeks.

Outcome Measures

The primary endpoint was the number of subjects with at least a 50% decrease in the target lesion score or in the PASI score. The secondary endpoints were the minimum PASI score, total erythema score, total induration score, total desquamation score, severity of itching, global assessment of activity.

The sponsor agreed to specify PASI score and physician global assessment score as main outcome criteria. PASI score of selected skin lesions would be a secondary outcome measure.

Clinical and Laboratory Assessments

Enrollment (≤ 28 days): history and physical; ECG; urinalysis; chemistry; hematology; PT; leukocyte subsets; pregnancy test; HCV, HBV, HIV testing; skin testing for delayed hypersensitivity; serum IgG, IgA, and IgM; serum isohemagglutinin; serum C3 and C4. In a subset of subjects skin biopsy and lymphocyte proliferation assays would be done.

Before each dose: physical exam; leukocyte subset analysis; hematology; chemistry; urinalysis; pregnancy testing; PASI, target skin lesions and itching assessment.

After each dose: at 1,4, 8, and (if available) 24 hrs: hematology and leukocyte subset analysis. Subjects would be followed for eight weeks after the last dose.

Photography of skin was done monthly. Pharmacokinetic sampling was done before and at 0.5, 8, 24 hrs after each infusion and at 7, 14, 28 and 56 days after the last infusion. Anti-BG9273 antibody testing was done.

The sponsor agreed to follow subjects until substantial (at least 75% of baseline) recovery of leukocyte subsets and CD2+ staining intensity was documented.

Case Report Form

The sponsor agreed to capture data on all infections using a check-off form in the CRF.

Results and Discussion

Thirty-three subjects entered the study. Three subjects in the second dose group withdrew, one for an adverse event, two for "other reasons" (reason not otherwise specified). Patients were considered responders if they experienced ≥50% reduction in PASI. By these criteria, seven patients responded during the treatment period and seven during the follow-up period.

There were two serious adverse events judged to be unrelated to study treatment: cholecystitis followed by uncomplicated cholecystectomy (0.025 mg/kg group) and chest pain ultimately diagnosed as GI in origin (0.5 mg/kg group). There was a suggestion of dose-dependent increase in adverse events associated with infection. None of the infections was serious and none was associated with lymphopenia or neutropenia.

Except for the subjects in the lowest IV dose and in the IM dose group, all other subjects experienced transient reduction in CD3, CD4 and CD8 T lymphocytes that returned to normal. Neutrophil counts increased in three subjects and platelet counts decreased in two subjects. One subject (0.05 mg/kg) had low-titer anti-alefacept antibodies at baseline and during study.

Skin hypersensitivity testing (**Table 4**) showed the following shifts from baseline to post- treatment.

- Positive to negative: tetanus (N=8), diphtheria (N=2), candida (N=3), tricophyton (N=1) and proteus (N=3).
- Negative to positive tuberculin (2).
- No shifts: streptococcus and glycerin (all were negative at baseline and remained negative post-treatment.

Table 4. Shift table. Skin testing of Delayed-type Hypersensitivity

		0.005 mg/kg IV		0.025 mg/kg IV		0.05 mg/kg IV		0.075 mg/kg IV		0.05 mg/kg IM	
		Post-treatment		**Post-treatment**		**Post-treatment**		**Post-treatment**		**Post-treatment**	
		+	-	+	-	+	-	+	-	+	-
Tuberculin	**Baseline** +	0	0	0	0	0	0	0	0	0	0
	-	1	4	0	5	0	8	1	5	0	6
Candida	**Baseline** +	0	0	0	2	0	0	0	0	0	1
	-	0	5	0	3	0	8	0	6	0	5
Tricophyton	**Baseline** +	0	0	0	1	0	0	0	0	0	0
	-	0	5	0	4	0	8	0	6	0	6

Proteus	**Baseline** +	2	0	1	1	1	1	0	0	0	1
	-	0	3	0	3	0	6	0	6	0	5
Tetanus	**Baseline** +	3	0	2	3	2	4	2	0	0	1
	-	0	2	0	0	0	2	0	4	0	5
Diphtheria	**Baseline** +	0	0	0	1	1	0	0	1	0	0
	-	0	5	0	4	0	7	0	5	0	6
Strep	**Baseline** +	0	0	0	0	0	0	0	0	0	0
	-	0	5	0	5	0	8	0	6	0	6
Glycerin control	**Baseline** +	0	0	0	0	0	0	0	0	0	0
	-	0	5	0	5	0	8	0	6	0	6

Reviewers' Comments:
The investigators used the MULTITEST CMI for skin testing. The protocol contained detailed instructions for application of the antigens to non-lesional skin and for reading the results. Induration greater than 2 mm in diameter was considered positive. The data listings show dichotomous readings of "positive" or "negative" for individual patients.

The significance of the antigen testing results is not clear. The shifts from positive to negative reaction are not dose dependent. However, the shifts do not appear to be random because they were not associated with corresponding shifts from negative to positive reaction. The only shifts from negative to positive were the two tuberculin shifts, one isolated, the other associated with a positive to negative reaction shift for another antigen. The maximum number of antigen shifts in one patient (04204) was three. Three patients (05-303, 304 and 306) who shifted from positive to negative for tetanus antigen were retested; one patient retested positive and two patients retested negative.

PROTOCOL C96-705
Title of Study
A randomized, double-blind, dose-escalation study to evaluate the tolerability, pharmacokinetics, biologic activity and efficacy of BG9273 (LFA-3/IgG1 Fusion Protein) when given once every 4 weeks for two doses in subjects with chronic Psoriasis.

Study Design
Multicenter, randomized, double-blind, dose-escalation study of IV infusion of 0.05, 0.10, 0.15 mg/kg BG9273.

Enrollment Criteria
Inclusion: Men and women, aged between 21 and 70, with moderate to severe, chronic plaque-type or palmar plantar psoriasis.

Exclusion: current erythrodermic or palmar pustular psoriasis; fever or symptomatic viral or bacterial infection; serious local or systemic infection; prior treatment with systemic retinoids within 8 weeks or immunosuppressant agents within 4 weeks prior to first dose.

Primary Outcome
Proportion of subjects with at least 50% reduction in PASI at any time during the study.

Clinical and Laboratory Assessments
Alefacept concentration, DTH, anti-alefacept antibodies, clinical labs, adverse events, PASI.

Study Conduct
The study was conducted in Europe (3 sites in UK and two in Hungary) and was run by BRI International. There were several serious protocol violations. There were concerns with timeliness, consistency and quality of flow cytometry measurements of lymphocyte subsets at two study centers. Fifteen subjects received major concomitant antipsoriatic treatment (e.g. PUVA, UVB, systemic corticosteroids) because of lack of psoriasis improvement. This further complicated the interpretation of safety data and confounded the activity data. Four subjects did not receive the intended dose due to pharmacist's errors. Few patients had low baseline PASI scores. The sponsor terminated the study prematurely because of the protocol violations.

Results and Discussion
Patient Disposition
19 subjects enrolled; 18 were dosed in the following dose groups: 6 with 0. 05 mg/kg, 6 with 0.10 mg/kg, 1 with 0.125 mg/kg, 5 with 0.15 mg/kg. 13 subjects completed, 1 was withdrawn due to an adverse event, and 4 were discontinued early following the sponsor's decision to terminate the study early. Participants were Caucasian, aged between 26 and 64, of whom 16 were men. PASI scores ranged from 5 to 38.

PASI
Treatment response was modest and was confounded by concomitant antipsoriasis medication use. Five subjects who responded were excluded from analysis because of use of antipsoriatic therapy (four received PUVA, one received betamethasone). Five subjects (26%) met the modest response criteria (>50% reduction in PASI anytime during study). Most of the responders were in the 0.1 mg/kg dose group.

Lymphocyte Counts
Table 5 shows that the incidence and severity of decreased lymphocyte counts were not clearly dose-dependent.

Table 5. Subjects with CD4+ and CD8+ Counts Below Specified Thresholds

	0.05 mg/kg N=6[a]	0.1 mg/kg N=6	0.125 mg/kg N=1	0.15 mg/kg N=5
CD4 <300	2	2	1	3
CD4 <200	0	1	0	1
CD8 <200	3	3	1	4
CD8 <100	1	1	0	1

[a]Subjects dosed

Two subjects in 0.1 mg/kg group had a prolonged depression in CD4+ lymphocyte counts following administration of their second dose of BG9273 (23-92 days below $300x10^6$ cells/μL) UV therapy was initiated 4 weeks after end of treatment confounding interpretation.

Infections

One subject in the 0.15 mg/kg group had culture-negative pyuria 2 weeks after the second dose. The pyuria was considered moderate and likely to be related to study drug. The subject was treated with nitrofurantoin. Neutrophils and lymphocytes were normal. Two subjects experienced rhinitis and flu-syndrome.

Serious Adverse Events

There were three serious adverse events, namely hospitalizations for treatment of psoriasis. Subject 05113 and 05204 were hospitalized for "treatment of psoriasis"; both events occurred after the end of the treatment period and were considered unrelated to alefacept. Subject 06305 developed pustular psoriasis four days after his first dose (0.15mg/kg) of alefacept. He had a low lymphocyte count at admission. His skin lesions grew *Staph hemolyticus*. Alefacept was discontinued and he was treated with antimicrobials, corticosteroids and retinoids. The subject recovered and the lymphocyte count returned to normal. The event was considered likely related to alefacept.

Delayed Hypersensitivity Testing

The sponsor cites one subject (05302) in the high dose group with a shift from positive to negative for one antigen.

Reviewers' comments

Seven antigens and one control were applied to non-lesional skin before and after alefacept dosing. Overall there were 7 shifts from positive to negative in individual antigens. There were two shifts from negative to positive. These shifts are isolated and are not related to dose. Similar trends in shifts were observed in a previous study.

PROTOCOL C98-709

Study Title

A Randomized, Multiple-Dose, Dose-Escalation Study to Determine the Relationship of Tolerability to Dose and Plasma Concentration of BG9712 (LFA-3/IgG1 Fusion Protein) in Subjects with Moderate to Severe Plaque Psoriasis

Study Objective
Determine activity safety and PK/PD of a new alefacept drug substance (BG9712) administered in multiple doses as an IV bolus, an IM injection, or an SC injection to patients with moderate to severe plaque psoriasis.

Study Design
Non-controlled, multi-center, randomized, double-blind, dose-escalation study of BG9712. The routes of administration were evaluated in a parallel fashion. The protocol contained appropriate dose-escalation rules.

Dosing
Once weekly for 12 weeks taking into account bioavailability results of previous studies:
IV bolus of 0.15, 0.225, 0.375,
IM injection of 0.15, 0.225, 0.375 mg/kg
SC injection of 0.15, 0.375, 0.75 mg/kg

Enrollment Criteria
Inclusion: Men and women aged between 18 and 70 years with moderate to severe plaque-type psoriasis. Normal absolute CD4+ lymphocyte count.
Exclusion: Erythrodermic, guttate, palmar, or plantar pustular, or generalized pustular psoriasis; fever or serious local or systemic infection (e.g., pneumonia, septicemia); prior treatment with systemic retinoids or immunosuppressants within 4 weeks prior to the first dose of study drug.

Primary Outcome
Proportion of patients with >75% improvement in PASI at two weeks after the end of treatment.

Clinical and Laboratory Assessments
PASI, PGA, target lesions. Adverse event reporting, physical examination, vital signs, ECG, hematology, peripheral lymphocyte subsets, immunoglobulins, isohemagglutinin, blood chemistry, urinalysis, determination of antibodies to LFA3TIP.

Protocol Amendments
Number of study patients was raised twice to final of 150. Two IV dose cohorts were added: 0.50, and 0.75 mg/kg.

Study Conduct
The study was terminated prematurely because of lower activity and poorer tolerability of BG9712 compared to historical data with BG9273

Patient Disposition
123 patients were enrolled and dosed: 69 received BG9712 IV, 30 by IM injection, and 24 by SC injection. There were 74 men (60%) and 49 women (40%), aged between 19 and 70 years, of whom 80% were Caucasian. Body weight ranged from 47 to 150 kg. In

the two highest IV dose group a high proportion of subjects (60-100%) did not complete treatment primarily due to decision to stop study for poor tolerability and lack of activity of BG 9712.

Results and Discussion

PK/PD

The mean volume of distribution was consistent with blood volume, half-life was around 270 hours, and bioavailability of IM and SC route was approximately 60%.

Reduction in lymphocyte counts induced by BG9712 was less marked than observed for BG9273 and was not dose-dependent. The mean total lymphocyte counts remained above the lower limit of normal at all time points and the proportion of patients with counts below thresholds was smaller. There were only sporadic occurrences of any patient dropping below 600 cells/ µL. Lymphocyte reductions were greater for the IV route than for the IM or SC routes. On average, counts had not recovered to the baseline level following treatment with BG9712. The SC treatment group was the slowest to recover. Changes in lymphocyte subsets observed with BG9712 (CD3, CD4, CD8) were qualitatively similar to those seen with BG9273.

Response to Treatment

Few (0-16% in each cohort, 3/39 overall) patients met the PASI 75 endpoint in the IV group. In the IM group 2/28 patients responded. In the SC group 5/22 patients responded. There was no evidence of dose response.

Safety

Up to 60% of patients in route of administration groups developed adverse events classified as infections. The most commonly reported Infection terms were; Infection (not specified), pharyngitis, sinusitis, and flu syndrome. There were 2 cases of herpes zoster and 2 of herpes simplex. Two patients ages 60-70, with long history of psoriasis and major antipsoriatic treatment had diagnoses of malignancy on study (a melanoma in situ and basal cell carcinoma). The lesions were noted at baseline.

Up to 50% of patients experienced symptoms (chills, headache, arthralgia, asthenia, myalgia, and nausea) after dosing in the 0.750 mg/kg IV dose group. Symptoms lasted <24 hrs. Similar symptoms were observed less frequently in the SC and IM groups.

Serious Adverse Events

Two serious adverse events were reported.

Cellulitis and septic shock (101-113.) (See Integrated Safety Summary, for narrative).

A 59 year old woman (127-123) developed chills, SOB, severe chest pain and vomiting following administration of alefacept. Gallstones were visualized and cholecystectomy was performed. The patient resumed alefacept dosing without recurrence of symptoms.

Patient Withdrawals

A 49-year old woman (106-107) developed zoster after 10 doses of 0.150 mg/kg IV and discontinued. *H. zoster* resolved in about 10 days.

Patient 111-113 discontinued because of fatigue, chills and joint aches after 0.75 mg/kg IV.

Reviewers' comments
The lower activity of the new product (BG 9712) was unexpected. The safety data raise clinical concerns similar to those in trials of BG9273. Questions arose about the reliability of potency assays and have been resolved. The sponsor stopped development of BG 9712.

PROTOCOL 98-710

Study Title

C98-710 (Version 3) "A Blinded, Multiple-Dose Study to Determine the Tolerability of Repeated Courses of LFA3TIP (LFA-3/IgG, Fusion Protein) in Subjects with Moderate, Moderate to Severe, or Severe Plaque Psoriasis"

Study Objectives

Determine the tolerability of repeated courses of LFA3TIP administered intravenously.
Determine if in subjects who complete study C97-708:

1. Responders (disease severity $\leq$ mild) retreated with the same dose of drug show similar or improved response.
2. Non-responders (disease severity $\geq$moderate) retreated with a higher dose of drug show a response.
3. Responders whose CD4 cell count was < 300/mm^3 on two consecutive visits show similar response when retreated with a lower dose of drug.

Study Design

Phase 2 multicenter, multiple-dose study in up to 228 subjects with plaque psoriasis who completed the post-dosing assessment in the C97-708 study (Visit 17). Investigators would be blinded to treatment allocation.

Reviewers' comments
A randomized controlled study would have been preferable. The sponsor agreed to assess safety and efficacy of retreatment in a future randomized blinded trial.

Study Treatment

Subjects received one of the following doses of LFA3TIP as BG9712 (0.0125, 0.025, 0.075, or 0.150 mg/kg) as an IV bolus once a week for a total of 12 doses per treatment course. Treatment allocation occurred according to the following criteria.

Group 1: Responders (received active drug and disease severity by "static" PGA at any time during the 12 week post-dosing period was mild, almost clear or clear) whose weekly CD4 count was not $\leq$300 cells/mm ^{3} on two consecutive visits. These subjects

were retreated using the same dose as in the C97708 study: (0.025, 0.075, or 0.150 mg/kg).

Group 2: Responders (received active drug and disease severity by PGA at any time during the 12 week post-dosing period was mild or better) who had CD4 counts < 300 cells/mm ^{3} on two consecutive visits. These subjects were retreated by dropping their dose to that of the next lower dose level.

Group 3: Subjects who received placebo during the C97-708 study. These subjects received a dose of 0.150 mg/kg of drug.

Group 4: Non-responders (received active drug and disease severity by PGA at any time during the 12 week post-dosing period remained moderate, moderate to severe, or severe) whose weekly CD4 counts did not drop to less than 300 cells/mm^3 on two consecutive visits. These subjects received one dose higher than that received during the C97-708 study to a maximum dose of 0. 150 mg/kg.

Reviewers' comments
Whereas subjects received alefacept as BG9273 in study 708, in the present study subjects received BG 9712. The objectives of the study were not realized because the clinical activity of BG9712 was lower than that of BG9273.

Concomitant Medications
No major antipsoriatic medications were allowed.

Modification of Treatment Schedule
1. Continuation of treatment required the following conditions be met:
   Administration of each dose of study drug separated by at least 7 days.
   No clinical evidence of viral or bacterial infection.
   Lymphocyte count within 24 h of dosing > 60% of LLN or > 50% of baseline.
   Absolute CD4 lymphocyte count from the previous week is >300 cells/mm^3.
2. Permanent discontinuation of treatment was required for the following reasons:
   Pregnancy, patient's choice, low CD4 count (< 300 cells/mm3) for >38 days between doses, medical emergency, investigator's choice.

Enrollment Criteria
Inclusion: Subjects would be eligible for retreatment following an increased disease severity. Subjects must have completed the C97-708 study (visit 17).
Exclusion: Subjects whose disease never improved to mild or better after the first treatment and whose CD4 count was <300 on two consecutive visits.

Evaluation of Safety
Safety was determined by changes in total lymphocytes and lymphocyte subsets, adverse events including infections, and laboratory abnormalities.

Efficacy Outcomes

Global assessment using both a static and a dynamic scale, PASI score, target lesion assessments, time to response, duration of response.

Clinical and Laboratory Assessments

Physical examination, vital signs, blood chemistry, blood count, urinalysis, lymphocyte subset analysis. Serum samples analyzed for descriptive pharmacokinetic parameters.

Results and Discussion

Pharmacodynamic Effects of BG9712

The results of the study are confounded by the lower biologic activity of BG9712 and by differences in baseline lymphocyte count between groups due to carry-over effects from alefacept treatment patients received in the previous study. **Table 6** shows the BG 9712 did not lead to drops below normal in lymphocyte counts in the highest dose group. Decreases in lymphocyte subsets (CD4+ and CD8+) were qualitatively similar to those seen in study 708. The drops were less pronounced than those seen with BG9273. No changes in B cells or NK cells were observed. The lack of dose proportionality in the decrease in lymphocyte counts is probably due to factors discussed above.

Table 6. Decrease in Lymphocyte Counts at Any Time During the Study

		0.025 mg	0.075 mg	0.125 mg
lymphocytes	>ULN	0/12	0/37	0/68
	<LLN	2/12 (17)	2/37 (5)	0/68
CD4 Count	>ULN	0/12	0/37	1/68 (1)
	<LLN	3/12 (25)	3/37 (8)	7/68 (10)
CD8 Count	>ULN	0/12	0/37	1/68 (1)
	<LLN	2/12 (17)	3/37 (8)	3/68 (4)

Response to Treatment

The proportion of responders (≥75 % improvement in PASI, PGA of "clear" or "almost clear") was low and dose dependent. Between 0 and 10% of patients were classified as responders in the three dose groups.

Reviewers' comments

In analyzing the efficacy data the sponsor did not consider as treatment failures patients who had received concomitant antipsoriatic therapy. Therefore, the actual response rates are likely to be lower. The agency did not reanalyze the efficacy data because the sponsor had stopped development of BG9712. Based on PD and efficacy outcomes it is reasonable to conclude that BG9712 appears to be less active than BG9273.

Safety

There were no deaths. One patient discontinued treatment due to recurrence of gingivitis. One patient developed low titer antibodies to alefacept.

Notable serious adverse events were;

- 27 year old in 0.15 mg group underwent fixation of comminuted tibial fracture 6 weeks after the end of 12-week course of alefacept. He developed infection at the

repair site requiring antimicrobials and re-operation. The event was judged to be resolved one week later.

- A 37 year old woman, had psoriasis for 15 years prior to study entry. She had previously received no systemic agents or phototherapy. She was allocated to the 0.15 mg/kg group and one month after start of dosing, a lesion on her back was biopsied and diagnosed as a squamous cell carcinoma (keratoacanthoma type). The patient's lowest lymphocyte and CD4+ count before the adverse event were 1130 cells/μL and 401 cells/L, respectively.

There was a suggestion of dose-dependent increase in the incidence of infections and of serious adverse events (**Table 7)**.

Table 7. Incidence of Infections and of Serious Adverse Events

	0.025 mg N=12	0.075mg N=37	0.15 mg N=68
Infectious adverse event	3 (25)	13 (35)	27 (40)
Serious adverse event	0	2 (5)	3 (4)

The more clinically significant infection terms listed were: abscess, cellulitis, conjunctivitis, epididimytis, herpes simplex, otitis externa, periodontal abscess, pneumonia, and urinary tract infection. The serious adverse events were: accidental injury, cholelithiasis, coronary occlusion, dysuria, hemorrhage, bacterial infection, and skin carcinoma.

Reviewers' comments
The safety profile of BG9712 raises clinical concerns similar to those raised by BG9273.

III. PHASE 2 AND 3 CLINICAL TRIALS

Table 8 lists the safety and efficacy studies.

Table 8. Phase 2 and 3 Safety/Efficacy Study Reports in the Original Submission

Study Title	Design (N)	Dosing	Objectives
C97-708: LFA3TIP in moderate to severe plaque psoriasis: a randomized, double-blind, placebo-controlled, parallel group, dose-response study	Blinded, randomized, dose- response, placebo controlled. N=229	BG9273 0.025, 0.075, 0.15 mg/kg weekly IV x 12 weeks	Safety, efficacy

C99-711: Randomized, double-blind, comparison of intravenous alefacept versus placebo in subjects with chronic plaque psoriasis	Blinded, randomized, placebo controlled. N=565	BG9273 7.5 mg weekly IV x 12 weeks (two courses)	Safety, efficacy of two 12-week IV treatment courses
C99-712: Randomized, double-blind, placebo-controlled, dose-comparison study of the efficacy and safety of intramuscular administration of alefacept in patients with chronic plaque psoriasis	Blinded randomized, placebo controlled. N=526	BG9273 10, 15 mg weekly IM x 12 weeks	Safety and efficacy of one 12 week IM treatment course
C99-714: Open-label study of tolerability and efficacy of repeat courses of alefacept in subjects with chronic plaque psoriasis who have completed study C97-708 or C98-709	Open label Retreatment. N=27 (ongoing)	BG9273 7.5 mg weekly IV x 12 weeks	Safety of repeated courses of alefacept

Issues Explored in the Efficacy Trials

Use of a Fixed Dose:

In healthy subjects (60-95kg) receiving a range of alefacept doses, clearance appeared to be dose independent. Body weight contributed little (5%) to the variability in alefacept concentration. Data from study C98-707 (N=23, 64-105kg) showed a relationship between body weight and alefacept concentration (R^2=0.7). Clearance varied two-fold (20 to 40 ml/hr) over the range of weights studied. In Study C97-708, body weight was not a significant covariate in effects of alefacept on CD4 lymphocyte count or severity of psoriasis determined by PASI score.

In view of the uncertainties regarding the relationship between dose, body weight and CD4 count, monitoring of lymphocyte counts before dosing was an essential component of dosing in the phase 3 studies. Conservative rules for dose interruption and/or discontinuation were used based on decrease in lymphocyte count and persistence of decrease.

Response to Retreatment:

Studies 711 and 712-717 were designed to evaluate the safety and efficacy of a second course of therapy. The response to treatment was evaluated by comparison to baseline before the start of the first treatment and before the start of the second treatment .

Duration of Treatment Response:

Following discontinuation of therapy psoriasis recurs. The duration of response varies with different therapies and is important information to include in the package insert. The sponsor defined duration of response as the time in which the patient is first found to be in response and the time at which the response was no longer maintained or the patient

started phototherapy or another systemic therapy. Both the start time and the stop time involved interpolation between the date of the visit in which there was less than a 75 % reduction from the baseline PASI score and the visit at which the patient had a 75% or greater improvement from the baseline PASI score.

Alternatively, duration of response can be defined to begin with the end of the treatment period and end with the last visit at which response was maintained. In this case duration of response excludes the interval during the treatment period. In addition, using this definition, the interval between visits is not used for imputation of duration of response. Patients who used antipsoriatic therapies after the end of study treatment are declared to have relapsed at the time of start of the antipsoriatic therapy (unless they were previously declared treatment failures).

The criteria for alefacept retreatment (PGA worse than mild) might have resulted in retreatment of a few patients who remained in response (PASI > 75% improvement) but did not achieve PGA score of mild. Rationale for low threshold for retreatment was the reluctance of some patients in previous studies to remain off therapy while deterioration occurred and the desire to explore potential for additional clearing in treatment responders. Patients who remained in remission and did not enter the second treatment period were censored at the last interim visit.

Long-term Treatment:
A conservative approach was used for testing repeated courses of alefacept therapy. Retreatment was separated by a minimum time interval of 3 months from first treatment for observation of safety and recovery of immune function.

Immune Function:
Alefacept induces lymphocyte depletion. There was evidence that complete recovery to baseline of lymphocyte subpopulations did not occur in certain patients. Important safety goals for the phase 3 studies were to follow study patients until adequate recovery of counts occurred (within +75% of baseline) and to determine if cumulative depletion of lymphocyte counts occurred upon retreatment. Evidence of clinically significant infections and neoplasms was carefully sought and correlated with lymphocyte counts. The relationship between decrease in PASI scores and CD4 counts was explored.

Experimental data: *in vitro*, animal, and human studies were designed to characterize effects of alefacept on immune functions (e.g. humoral and DTH responses).

Clinical Assessments of Psoriasis:
The concordance between various assessments of disease severity was evaluated in phase 3. At the time the clinical trials were designed questions had been raised about the usefulness of PASI. On March 20, 1998, the Dermatologic and Ophthalmic Drugs Advisory Committee (DODAC) discussed clinical trial design and analysis for studies of psoriasis. The committee discussed shortcomings of clinical scoring of disease severity and recommended that a global physician assessment scoring system be used as primary efficacy outcome. The committee recommended that substantial improvement (defined as $\geq$75%) be used to define clinical benefit. A responder analysis was recommended

identifying patients with improvement of 100% (completely cleared with restoration of normal skin markings), 90-99% (almost clear with no plaque or scaling and dull erythema, 75% clear (equivalent to a change in severity from severe to mild or from moderate to clear). The committee recommended that photography either of whole body or of target lesions be done. Close ups to show skin markings were recommended. The committee indicated that extended follow up will be needed to assess the safety of immunosuppressive agents.

In the phase 2 study a "static" physician global assessment was used as the primary efficacy measure. A 7-point scale was used to define disease severity and to assess the proportion of responders. The proportion of patients showing a decrease in PASI $\geq$ 75% was the most important secondary efficacy outcome. A formal analysis of the reliability of the PGA assessments was performed. Analyses of the phase 2 efficacy data showed concordance between PGA and PASI scoring. The PASI score was used as primary efficacy outcome in the phase 3 studies. PGA was used as the principal secondary outcome. Concordance between the two outcomes was shown in the phase 3 studies.

Factors Influencing Psoriasis:
US centers were to be pooled by geographic region: southwestern, midwestern, southeastern, and northeastern. The rationale was that ultra-violet light exposure might be higher at lower latitudes and at higher elevations and therefore influence response to treatment. Data from study C97-708 suggested a higher response rate for individuals who were naïve to prior therapy for psoriasis. Randomization would be stratified by baseline disease: PASI > 20 or < 20 and by previous treatment history (naïve or previously exposed to systemic antipsoriatic therapy).

Concomitant Antipsoriatic Medication:
There was considerable use of major antipsoriatic medications in the phase 2 study. This may have resulted in overestimation of response to treatment. In the phase 3 study patients using major antipsoriatic medications were considered treatment failures for the purpose of the efficacy analysis.

Pediatric Studies:
Treatment of children:
Biogen asked for and received a deferral of its obligation to carry out pediatric studies in the phase 3 program. DODAC on May 23, 2002 recommended obtaining additional safety data in adults before initiating trials in children.

PROTOCOL C97-708
Study Objectives
The objective of this study was to determine the relationship of clinical response to the dose and plasma concentration of BG9273 when administered once a week for a total of up to 12 doses to subjects with moderate to severe plaque psoriasis.

Study Design

Phase 2, multicenter (25 sites), randomized, double-blind, placebo-controlled, parallel-group, dose-ranging (0.025, 0.075, and 0.150 mg/kg IV once weekly for 12 weeks) study in up to 200 subjects with moderate to severe plaque psoriasis.

The placebo was saline (5 ml) administered by IV bolus. Subjects were randomized by site. The site pharmacists or the investigator's designee were unblinded to prepare doses of drug. One investigator at each site was unblinded only to subjects' hematology results. All other study personnel, including study coordinators and nursing staff, were to remain blinded. The physicians performing the efficacy assessments remained blinded at all times. All candidates screened for inclusion in the study were logged in. For subjects not enrolled into the study, the reason(s) for exclusion were documented.

Inclusion Criteria

Men or women between 18 and 70 years. Moderate to severe chronic plaque-type psoriasis as defined by a body surface involvement of 10% or greater, previous treatment with systemic or phototherapy and diagnosis for more than 1 year. Must have absolute CD4+ lymphocyte counts at or greater than the lower limit of normal within 14 days before the first dose. Subjects on any prescription medication must be on stable doses of that medication for at least 14 days before the first dose of study drug. Women must be postmenopausal for at least 1 year, surgically sterile, or willing to practice effective contraception.

Exclusion Criteria

Erythrodermic, guttate, palmar, plantar pustular, or generalized pustular psoriasis. Clinically significant abnormal laboratory values for hematocrit, hemoglobin, platelets, serum creatinine, or bilirubin. ALT and AST must not be greater than 3 times the upper limit of normal. History of anaphylactic reactions. History of clinically significant cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic, urologic, pulmonary, neurologic, psychiatric, renal, and/or other major disease (other than psoriasis). Serious local or systemic infection (e.g., pneumonia, septicemia) within the 3 months before the first dose of study drug. Fever (body temperature >38 C) or symptomatic viral or bacterial infection (including upper respiratory infection) within 2 weeks before the first dose of study drug. Positive for hepatitis C antibody or hepatitis B surface antigen. Positive for HIV antibody, or known to have risk factors for HIV infection. Morbidly obese (>75% above ideal body weight). Treatment with the following drugs before receiving the study drug: systemic retinoids within 4 weeks; systemic immunosuppressants (e.g., methotrexate, cyclosporine) within 4 weeks; oral prednisone >25 mg/day (or its equivalent) within 2 weeks; high potency corticosteroids, keratolytics or coal tar (other than on the scalp, palms, groin, and/or soles) within the 2 weeks; UV therapy within 2 weeks or anticipated need for UV therapy during the study period. Poor clinical response to cyclosporine or methotrexate after an adequate regimen and duration of treatment.

Dose Modification Rules

Administration of each dose of study drug would be separated by an interval of at least 6 days, but not greater than 14 days. The absolute lymphocyte count obtained at the site could be no less than 67% of the lower limit of normal within 24 hours before dosing. If study drug is withheld from a subject, placebo would be administered in lieu of the withheld dose of study drug. In the event that the absolute lymphocyte count was not greater than 67% of the lower limit of normal, the physician unblinded to hematology results would notify the pharmacist/designee to administer placebo instead of the study drug. The absolute CD4+ lymphocyte count from the previous week had to be >300 cells/mm^3.

Withdrawal of Subjects

Subjects were to be withdrawn for the following reasons: pregnancy, a 20 or more point increase in PASI score from baseline to 4 weeks; subjects' choice.

Concomitant Therapy

Moderate to high potency topical corticosteroids, keratolytics, coal tar, or calcipotriol were not permitted except on groin, scalp, palms, and soles. Low potency (class V) topical corticosteroids could not be used on target lesions. Subjects were instructed not to use emollients within 12 hours prior to visits and prior to evaluation of physician global assessments and PASI. The subject's sun exposure was to be limited during the entire study.

Clinical Efficacy Assessments

All efficacy assessments were to be performed by the same investigator for each subject. The primary efficacy outcome was the proportion of subjects who sustained for at least two weeks during the period between visits 11 and 17 a 75% or greater improvement in skin lesions as measured by physician global assessment.

The secondary efficacy outcomes were: Length of time the PASI remained 50% below baseline after the last dose of study drug; time to reduction in PASI score of at least 50% from baseline; time to 50% improvement in global physician assessment scale.

The tertiary efficacy outcomes were: Proportion of subjects who achieved a reduction of 75% from baseline in PASI sustained for at least two weeks during the interval between visits 11 and 17; proportion of subjects who achieved clear or almost clear on physician global assessment; QOL assessments; 75% improvement of target lesions.

Statistical Analyses

No sample size calculations were provided in the original protocol. The statistical method used to test a positive dose-response relationship for both global assessment and PASI was a Cochran-Armitage regression. Analysis of covariance was to be used to assess center by group interactions. The components of the PASI was assessed by Cochran-Mantel-Haenszel test statistic.

Clinical and Laboratory Assessments

All blood samples for hematology and lymphocyte subset analysis were collected at the same time of the day in order to prevent artifact of diurnal variation.

Baseline:

Complete medical history and physical examination including measurement of vital signs and body weight. Urinalysis, blood chemistries, hematology, pregnancy test for women, HCV and HIV Abs, HBsAg. Skin testing of delayed-type hypersensitivity with reading of results 48 hours later. Collection of blood for determination of antibody formation to BG9273. Analysis of peripheral lymphocyte subsets. Collection of blood for pharmacokinetic assay of BG9273 levels.

On study:

The following testing was done according to the schedule indicated:
Complete physical examination: visits 5, 9, 13, and 17. Vital signs: visits 1-13, and 15-17. Body weight: visits 1-13, and 15-17.Urinalysis: visit 15. Chemistries: visits 5, 9, 13, 15, and 17. Hematology: visits 1-13, and 15-17. Pregnancy test for women: visits 7, 13, and 17. Skin testing of delayed-type hypersensitivity for recall antigen: visits 13 and 17.Antibody formation to BG9273: visits 15 and 17. Photography visits 1, 7, 13, and 17. Investigator and subject global assessments of efficacy, PASI, target lesions, and pruritus: visits 1, 3, 5, 7, 9, 11, 12, 13, 14, 15, 16, and 17.Assessment of any ongoing or new viral, bacterial, or fungal infections: visits 2 through 19. Peripheral lymphocyte subsets: visits 1 through 13, and Visits 15, 16, and 17. BG9273 levels: Visits 3, 7, 12, 15, and 17; also to be obtained 30 minutes after study drug administration on Visit 12. Quality of life assessment: Visits 1, 7, 13, 15, and 17. Telephone monitoring to assess the subject's well-being to be performed weekly during post-dosing period (other than scheduled visits). Subjects would be contacted via telephone (Visits 18 and 19) to assess health status.

Study Results

Patient Disposition

Enrollment occurred between May and November of 1998. The study was completed on December 1999. There were 22 study centers; four centers (117, 121, 122, 127) enrolled about 20 patients each, comprising approximately one third of all study subjects.

Reviewers' comments

In these four study centers, the proportion of responders by treatment group was similar to that seen in the overall study patient population.

For the purpose of data analysis the study centers were pooled using post-hoc criteria. This resulted in grouping of subjects in the following geographic regions: SW, MW, SE, NE each containing approximately 55 subjects.

Table 9. Patient Disposition

	Placebo	0.025	0.075	0.150
RANDOMIZED	59 (100)	57 (100)	55 (100)	58 (100)
DOSED	59 (100)	57 (100)	55 (100)	58 (100)
DID NOT COMPLETE TREATMENT	10 (17)	6 (11)	7 (13)	9 (16)
Lost to Follow-up	1 (2)	2 (4)	0	2 (3)
Voluntary Withdrawal	3 (5)	0	1 (2)	5 (9)
Adverse Event	0	1 (2)	3 (5)	0
Laboratory Abnormality	0	0	1 (2)	1 (2)
Worsening of Disease	5 (8)	2 (4)	1 (2)	0
Other	1 (2)	1 (2)	1 (2)	1 (2)
WITHDRAWN FROM TREATMENT	4 (7)	4 (7)	3 (5)	5 (9)
Lost to Follow-up	2 (3)	2 (4)	0	2 (3)
Voluntary Withdrawal	2 (3)	1 (2)	2 (4)	3 (5)
Other	0	1 (2)	1 (2)	0
EXCLUDED FROM EFFICACY ANALYSIS[a]				
Center 117	5	5	5	5
Center 122	4	5	5	5
POPULATION FOR EFFICACY ANALYSIS	50	47	45	48

[a]Data excluded for violations of Good Clinical Practices.

The proportion of subjects who discontinued study treatment was numerically higher in the placebo (N=17) and high dose (N=16) groups compared to low (N=11) and mid-dose groups (N= 13). Six subjects (five in the mid and high dose groups) discontinued treatment for adverse events or laboratory abnormalities. The proportion of subjects who discontinued study treatment for worsening of disease was numerically highest in the placebo group (**Table 9**).The proportion of subjects who did not receive all 12 treatments was high and was comparable across treatment groups (83-89%). The proportion of subjects who had one or more study treatments substituted with placebo was dependent on dose and was 2% in the placebo group and 8, 27, 51% respectively in the low, mid, and high dose groups.

Demographics

The following demographic factors and baseline disease characteristics were not well balanced across groups: age, ethnic origin gender, severity of psoriasis and history of anti-psoriatic treatments (**Tables 10** and **11**.) These imbalances included factors that do not predict response to treatment, were not associated with any specific group and were judged to be due to small sample size. Study patients had a median age of around 45 years, were predominantly men (60-80%), mostly Caucasian in origin (82-95%). The median body weight was 100 kg and ranged from 58 to 158 kg.

Disease Characteristics at Baseline

Median duration of disease was 15-20 years (range 1-62 years). The proportion of patients treated with various phototherapies and systemic therapeutic agents was numerically lower in the low dose group (**Table 10**).

Table 10. Onset of Psoriasis and Prior Treatment

	PLACEBO	0.025	0.075	0.150
DOSED	59 (100)	57 (100)	55 (100)	58 (100)
AGE: Median (yrs	42	50	44	44
GENDER: Women	24 (41)	12 (21)	14 (25)	16 (28)
Men	35 (59)	45 (79)	41(75)	42 (72)
ETHNICITY:				
Black	1 (2)	0	1 (2)	1 (2)
Caucasian	56 (95)	50 (88)	45 (82)	48 (83)
Asian	2 (3)	1 (2)	1 (2)	0
Hispanic	0	6 (11	8 (15)	8 (14)
Other	0	0	0	1(2)
Psoriasis Onset				
Median (yrs)	18	15	19	18
Min.-Max. (yrs)	1-40	3-38	1-59	2-62
Prior Treatment				
UVB	22 (37)	24 (42)	20 (36)	29 (50)
PUVA	22 (37)	12 (21)	18 (33)	20 (34)
Methotrexate	15 (25)	9 (16)	14 (25)	13 (22)
Retinoids	14 (24)	10 (18)	8 (15)	7 (12)
Cyclosporin	2(3)	0	5 (9)	1 (2)
Hydroxyurea	0	1 (2)	0	1 (2)
Thioguanine	0	0	0	1 (2)
Rapamycin	0	0	0	1 (2)
OVERALL	43 (73)	34 (60)	39 (71)	41 (71)

Psoriasis was more severe at baseline in patients in the high dose group as shown by the following criteria (**Table 11**). The median percentage of body surface area affected by psoriasis was 25% in the high dose group compared to 20% in other two treatment groups; the proportion of patients with psoriasis "moderate-to-severe" or worse was 57% in the high dose group compared to 37-46% in the other groups; the proportion of patients with PASI score $\geq$ 20 was 48% in the high dose group compared to 21-25% in the other groups.

Table 11. Baseline Disease Characteristics

	Placebo (N=59)	0.025 (N=57)	0.075 (N=55)	0.15 (N=58)
% Surface Area Involved [a]	20 (10-80)	20 (10-90)	18 (10-85)	25 (10-85)
Static Global Assessment [b]				
Severe	6 (10)	7 (12)	5 (9)	5 (9)
Moderate to Severe	21 (36)	14 (25)	18 (33)	28 (48)
Moderate	21 (36)	30 (53)	27 (49)	20 (34)
Mild to Moderate	10 (17)	5 (9)	4 (7)	5 (9)
Mild	1 (2)	1 (2)	1 (2)	0
Almost Clear	0	0	0	0
Clear	0	0	0	0
PASI Score [b]				
< 5	2 (3)	4 (7)	1 (2)	0
5 -9.9	11 (19)	11 (19)	12 (22)	12 (21)

10 -19.9	34 (58)	28 (49)	28 (51)	18 (31)
20 -29.9	9 (15)	9 (16)	10 (18)	20 (34)
30 -39.9	1 (2)	2 (4)	3 (5)	5 (9)
40 -49.9	1 (2)	3 (5)	1 (2)	2 (3)
50- 70	1(2)	0	0	1 (2)

[a] medians (min- max)

[b] N (percentages)

The severity of psoriasis was classified using a five-point global assessment scale (1=mild, 5=severe). About 90% of subjects were classified as having moderate-or-worse disease at baseline. Cross correlation between the global assessment and PASI scores showed broad overlaps between the categories. The greatest heterogeneity was in the "severe" disease category in which individual patient PASI scores ranged from 8 to 72.

Study Conduct

Table 11 shows that overall about 20% of study patients were not eligible for entry into the study because of mild psoriasis (defined as <10% BSA involvement).

Nearly 80% of patients received one or more antipsoriatic therapies during the study. The protocol allowed use of any topical antipsoriatic therapies (with the exception of retinoids). Application was to be limited to groin, scalp, palms and soles. About 10% of patients received non-allowed anti-psoriatic therapies (including systemic therapy and phototherapy).

Protocol Deviations

The study report (Section 10.4) cites the following violations of study protocol: enrollment of patients with "mild" psoriasis at baseline, missed study treatments, use of non-allowed concomitant medications, schedule evaluations missed or performed outside the allowed time window. The report lists the following individual violations in the placebo group: two subjects had acute infections within 2 weeks of study entry, one subject was morbidly obese, one subject had insufficient washout from systemic retinoid therapy. In the active groups one subject was morbidly obese.

The written report contains no tabulation of protocol deviations. No listing of deviations is found in the study report appendix; section 16.2.2 (Protocol Deviations) contains only the following statement "Not Applicable". CRT and statistical data sets and data definition tables do not contain this data set. The statistical programs do not contain a program for deriving these data.

The sponsor audited center 122 (Irvine Clinical Research Center) and determined that serious violations of good clinical practice had occurred. As a result, the principal investigator and the study coordinator were withdrawn from the study. The agency conducted its own audit and found missing documentation of the sources for CRF data. Examples were lack of documentation that the physician had attended the clinic on certain patient visit days when assessments of psoriasis were entered in the CRF, and lack of documentation that measurements of vital signs entered in the CRF were performed by the study coordinator.

At center 117, the sponsor found discrepancies between PASI score, static PGA and photography of skin lesions. The sponsor determined that the investigator had misunderstood the procedure for assessing static PGA. Efficacy data from study centers 117 and 122 was excluded from the primary analysis. Sensitivity analyses of the primary efficacy outcomes using data from both study centers revealed the relative proportion of responders across groups similar to the overall study primary efficacy analysis.

Use of Concomitant Medications

Table 12 shows that there was considerable use of potent antipsoriatic medication during the study. This is a significant concern because of potential confounding effects on at least some of the efficacy outcomes.

Table 12. Concomitant Therapy for Psoriasis

	Placebo 59 (100)	0.025 mg 57 (100)	0.075mg 55 (100)	0.15 mg 58 (100)	Total 229 (100)
Concomitant anti-psoriatic use	23 (39)	14 (25)	15 (27)	13 (22)	65 (28)
Topical steroids					
Mild: cortisone	10 (17)	5 (9)	7 (13)	3 (5)	25 (11)
Moderate: derma-smoothe-fs	0	0	1 (2)	0	1 (<1)
Potent:	5 (8)	4 (7)	4 (7)	4 (7)	17 (7)
clobetasol propionate	3 (5)	3 (5)	2 (4)	2 (3)	10 (4)
fluocinonide	1 (2)	0	1 (2)	2 (3)	4 (2)
diflorasone diacetate	1 (2)	0	1 (2)	0	2 (<1)
halcinonide	0	1 (2)	0	0	1 (<1)
Superpotent	1 (2)	0	1 (2)	2 (3)	4 (2)
betamethasone dipropionate	1 (2)	0	0	1 (2)	2 (<1)
ulobetasol propionate	0	0	1 (2)	1 (2)	2 (<1)
Systemic treatment and phototherapy	13 (22)	7 (12)	5 (9)	5 (9)	30 (13)
methotrexate	5 (8)	2 (4)	2 (4)	1 (2)	10 (4)
prednisone	1 (2)	3 (5)	1 (2)	1 (2)	6 (3)
UVB	1 (2)	1 (2)	2 (4)	1 (2)	5 (2)
cyclosporin	2 (3)	1 (2)	0	1 (2)	4 (2)
acitretin	2 (3)	1 (2)	0	0	3 (1)
methylprednisolone	0	0	1 (2)	1 (2)	2 (<1)
PUVA	2 (3)	0	0	0	2 (<1)
methylprednisolone acetate	1 (2)	0	0	0	1 (<1)
methylprednisolone sodium succinate	0	1 (2)	0	0	1 (<1)
psoralens for topical use	1 (2)	0	0	0	1 (<1)

Reviewers' comment

The large number of patients on concomitant antipsoriatic treatments is notable. Accounting for start and duration of treatment, and (in the case of topical therapy)

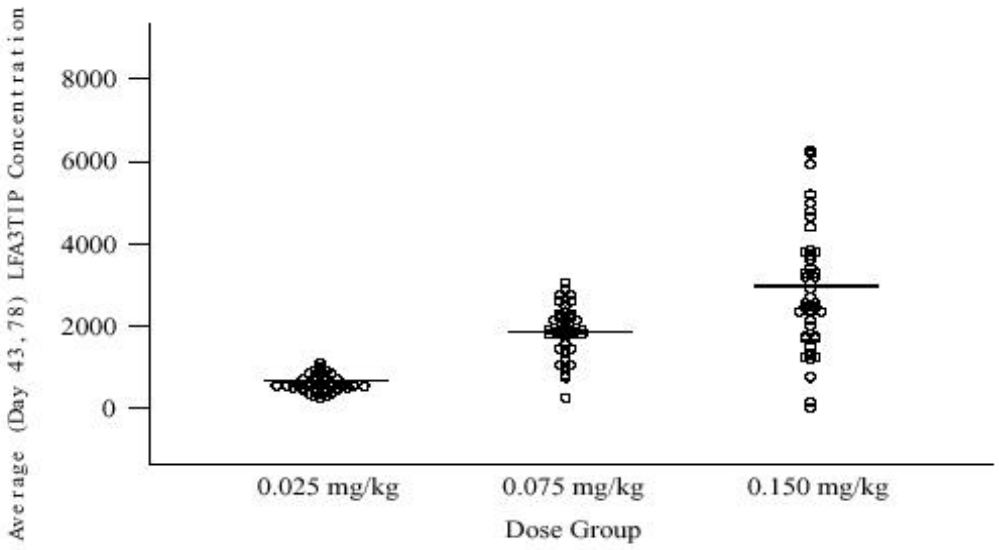
application site(s) was difficult. Certain treatments (e.g. PUVA, UVB, methotrexate, cyclosporin) were not allowed by the protocol.

Study Outcomes: Pharmakokinetics

Comparison of alefacept concentration in paired serum samples obtained at treatment days 43 and 73 showed variability in individual patients within each dose group. Overall the data showed no evidence of alefacept accumulation at the later time point.

With the assumption that steady state was achieved at treatment day 48, the sponsor compared mean alefacept concentrations between treatment groups (See **Figure 3.4-2** below). Serum concentration of alefacept increased with administered dose. There was considerable variability in the mid and high dose groups. Particularly in the 0.15 mg/kg dose group withholding of alefacept dosing due to lymphopenia may have contributed to the variability; in this group 50% of patients did not have paired serum samples available for analysis. The sponsor also attributes the variability in alefacept concentrations to the wide range in body weight of the study subjects; no supporting data are shown.

Figure 3.4-2 Distribution of alefacept concentrations in Study 708



Each symbol represents value for a single subject (average of Days 43 and 78 pre-dose values), the horizontal line indicates the mean for the treatment group.

Primary Efficacy Outcomes

The primary efficacy analysis was to be performed in the intent to treat population defined as all subjects randomized and receiving at least one dose of study treatment. The evaluable population was defined as all randomized subjects receiving $\geq$ 8 doses of study treatment. The primary efficacy outcome was the proportion of subjects experiencing sustained (defined as $\geq$2 weeks) improvement of 75% or greater in psoriasis measured by static physician global assessment. The time to achieve endpoint could be anytime

between visit 12 (end of treatment) and visit 17 (12 weeks post-treatment). Any center with < 16 randomized subjects was to be pooled into a single center. A Cochran-Armitage regression was used to look for a positive dose-response relationship for the primary efficacy outcome (75% improvement by PGA) and for the principal secondary outcome (75% improvement in PASI). The regression model was: response (0,1) = intercept + slope for dose response x log (dose).

On May 14, 1998 the primary outcome was changed to the proportion of subjects whose disease severity was mild or better (mild, almost clear, or clear) as measured by global assessment at 2 weeks after the last dose of study drug. The principal secondary outcome was an analysis of subjects who improved from: a) "severe" or "moderate-to-severe" to "mild" or b) "moderate" to "almost clear" or "clear".

The modeling approach presented by the sponsor for the primary analysis differs from the pre-specified plan. The following are the main differences.

1. Baseline characteristics that differed (<0.05) between groups (including newly defined geographic regions) were added to the analysis model.
2. Pooling of centers was based on geographic regions.

   Pooling of centers with <16 subjects (as pre-specified) led to one large pooled center and four individual centers. The sponsor developed a post-hoc system of pooling centers based on four geographic regions (Southwest, Midwest, Southeast, Northeast). Each region contained 4-7 individual study centers and 45-62 subjects.

At Week-2 post-treatment the p value for linear dose response = 0.053 with the post-hoc inclusion of geographic region in the analysis model. The sponsor found significant p values for dose-dependency of treatment response using secondary post-treatment time points and/or using secondary efficacy outcomes. However, in these analyses the problem of multiplicity is not addressed. The sponsor also analyzed dose response by treatment cohorts defined by measured alefacept serum concentrations. The results of these analyses in general support the notion of a dose-dependent treatment response. The response does not appear to be linear. The hypothesis testing results of a sensitivity analysis excluding geographic region from the model are consistent with the primary analysis.

The primary efficacy outcome of improvement in static physician global assessment showed evidence of a modest treatment effect (**Table 13**). The proportion of responders was approximately 20% (absolute) higher in the alefacept treated groups compared to placebo. The presence of a treatment effect of similar magnitude was evident using the secondary efficacy outcome of 75% reduction from baseline in PASI score.

Table 13. Proportion of Responders by Dose Group at Follow-up Week 2

	Placebo	**0.025 mg/kg**	**0.075 mg/kg**	**0.150 mg/kg**
Primary outcome: PGA "mild or better"	5/45 (11)[a]	14/42 (33)[a]	15/41 (37)[a]	14/41 (34)[a]
	5/50 (10)[b].	14/47(30)[b]	15/45 (33)[b]	14/48 (29)[b]

better"	----	4.3 (1.3, 14)[c]	4.6 (1.5, 14)[c]	3.8 (1.22, 12)[c]
Secondary outcome: PASI ≥75%	5/55 (9)[d]	10/52 (19)[d]	15/50(30)[d]	14/53 (26)[d]
	-----	2.6 (0.8, 8.4)[c]	4.36 (1.4, 13)[c]	3.69 (1.2, 11)[c]

[a]Proportions excluding missing data
[b]Proportions for intent to treat population ; centers 117 and 122 are excluded.
[c]Odds ratio (95% C.I.) of the respective treatment group over placebo based on the intent-to-treat population.
[d]Center 122 is excluded

There were minor discrepancies in the proportion of responders based on the definition of intent to treat population and on handling of missing data. **Table 13** shows the proportion of responders using subjects randomized who received at least one dose of study drug, excluding centers 117 and 122 and considering subjects with missing data treatment failures. The proportions meeting the primary efficacy outcome (PGA mild or better) were 10 % in placebo and about 30% in the alefacept groups. The proportions meeting the principal secondary outcome (≥75% decrease in PASI) were similar.
The study captured several secondary outcomes that are based on the same cardinal disease manifestations of psoriasis. As expected these outcomes also showed evidence of a treatment effect.

Reviewers' comment
The protocol did not require that patients who received concomitant anti-psoriatic therapy be considered non responders for the efficacy analyses. This may have led to an overestimate of the response to alefacept treatment. Alternatively, if more placebo patients received concomitant anti-psoriatic treatment on study, it could minimize the magnitude of the treatment difference.

At two weeks post treatment the mean percentage change in PASI compared to baseline was approximately 30% in the placebo group and 40-50% in the alefacept groups. Within each group, the induration, erythema and desquamation components of the score all declined in parallel (**Table 14)**. An analysis of change in disease manifestations without weighting for area gave similar results. Assessment of target lesions also confirmed the presence of a treatment effect in the two anatomic regions examined (trunk and limbs). Overall responses were numerically higher in the trunk compared to the limb lesions.

Table 14. Mean % Change in PASI Components at 2 Weeks Post Treatment

	Placebo	**0.025**	**0.075**	**0.150**
Number of subjects *	49	47	45	45
% change PASI	-21	-38	-53	-53
Induration	-22	-34	-54	-57
Erythema	-20	-35	-50	-47
Scaling	-17	-38	-48	-52

* Excludes Center 122

Study 708 provided evidence of treatment effect. The study did not provide sufficient information about relative activity of the doses tested. The sponsor categorized study patients based on alefacept concentration data into quartiles (0-100, 125-285, 835-2000, and 2250-8100 ng/ml). The sponsor analyzed response variables based on post-hoc allocation of patients to one of four alefacept concentration groups. The results of these analyses were compared to the results of the pre-specified efficacy analyses based on treatment allocation.

Some analyses of treatment response performed by the sponsor suggested overlap in the proportion of responders in the two top dose groups and numerical separation of mid and high dose group from the low dose group. Other analyses (e.g. by drug concentration quartiles) suggested virtual overlap in proportion of responders in low and mid dose groups and numerically higher proportion of responders in the high dose group. (See **Figures 11-3** and **11-4** below).

Figure 11-3 Primary Endpoint (PGA Mild or Better) by Dose and Time

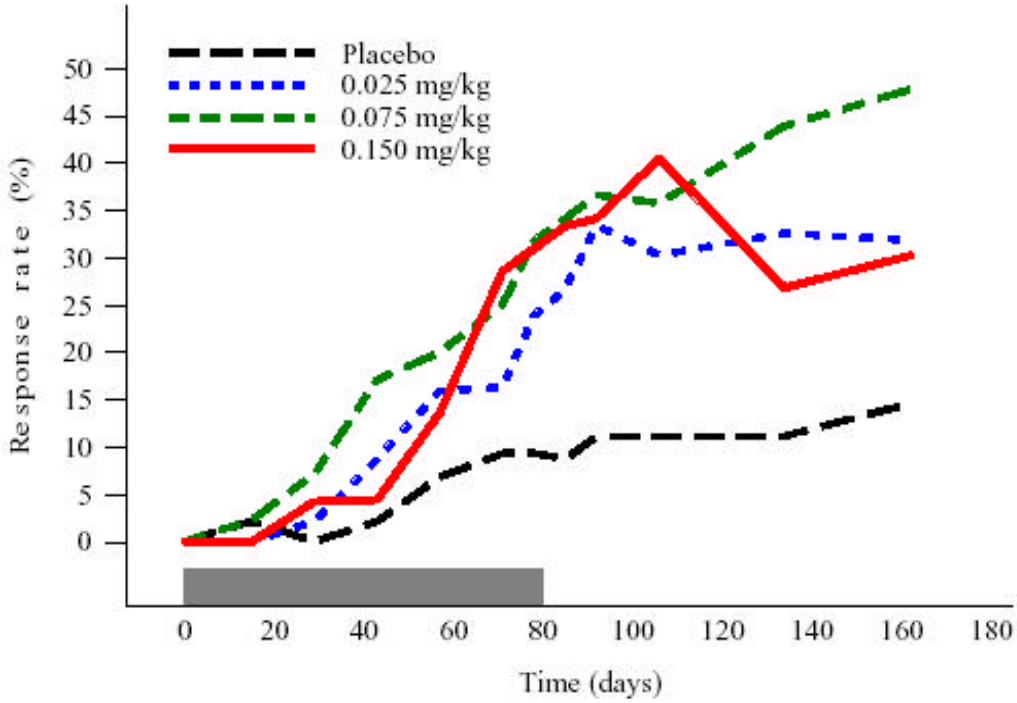
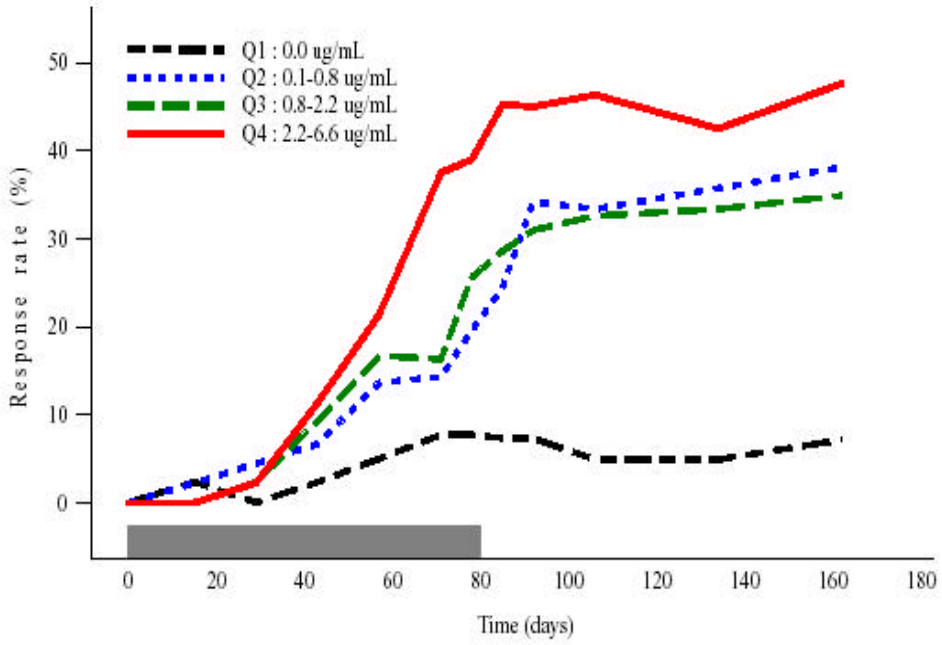


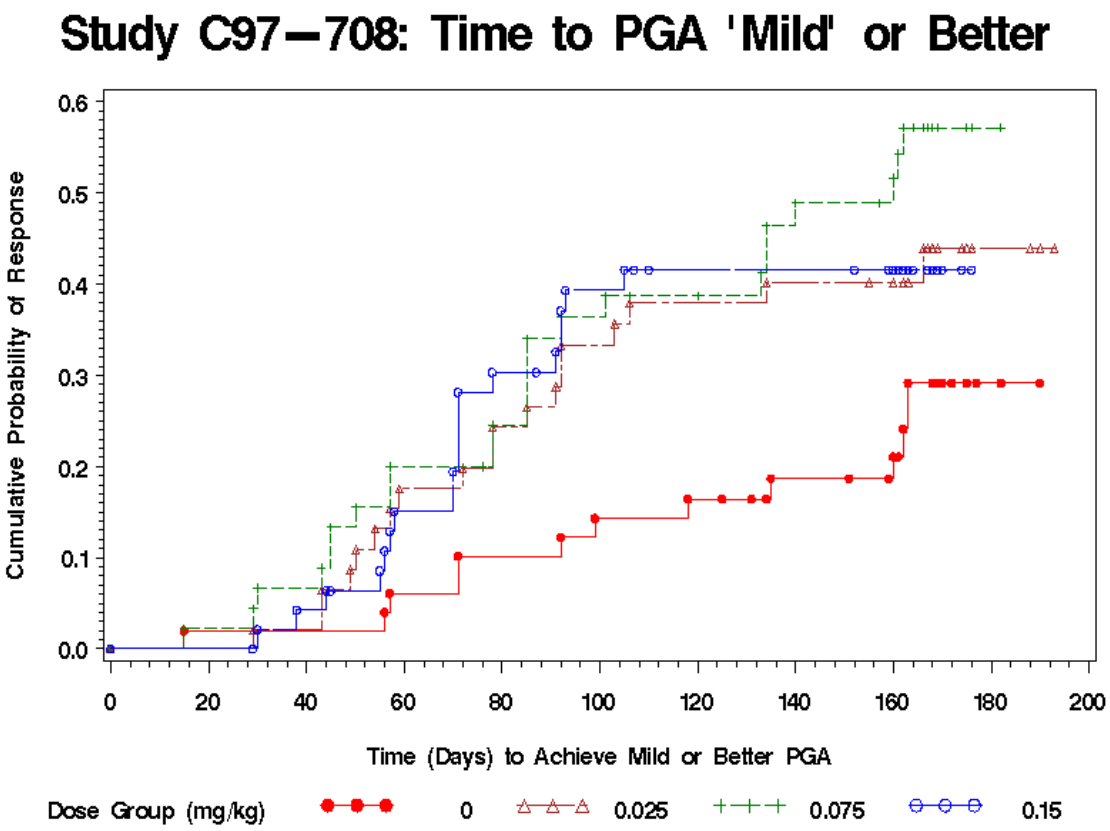
Figure 11-4 Primary Endpoint (PGA Mild or Better) by Concentration and Time



Secondary Efficacy Outcomes

Time-to-response and duration of treatment response

Additional useful analyses in per-protocol treatment responders is time to response (during the treatment period), and duration of response (after the end of the treatment period) by treatment group. It is worth noting that these analyses may be confounded by the disallowed concomitant medications patients received for psoriasis. The sponsor defines duration of response as the number of days between onset of response and the next observation in which the subject no longer meets the response criteria. The sponsor added 7 days to the duration if the response ended on or before week 2 post treatment and 14 days if the response ended after week 2 post treatment. The sponsor states that the time to onset of response occurs significantly earlier in the alefacept groups compared to placebo (See **Kaplan Meyer plot** below).



Reviewer's comments
Separation between the alefacept groups and placebo curves began relatively late (after day 60) during the treatment period, the number of responders is very small, there was no difference between the three alefacept groups. For these reasons, the significance of the difference in time to response between alefacept and placebo is not clear.

With regard to duration of response, the sponsor found no difference in duration of response during treatment and an overall difference between alefacept and placebo after the treatment period (**Table 15**).

Table 15. Duration of Response (days) PGA Mild or Better

	Placebo	0.025	0.075	0.15	Diff	Linear
DURING TREATMENT PERIOD					0.32	0.67
N	5	11	13	15		
Median	28	28	42	14		
Min – Max	11-41	7-44	7-84	7-58		
DURING FOLLOW-UP					0.025	0.006
N	11	17	23	17		
Median	29	91	89	89		
Min – Max	14-91	7-140	14-101	28-107		

'Diff' represents the p -value for overall treatment differences; 'Linear' represents the p -value for linear dose-response.

Reviewer's comments

Duration of response during the treatment period is not as clinically meaningful an outcome measure as response at the end of treatment or duration of response after discontinuation of treatment. Nevertheless, there are no differences between groups. This observation does not support the sponsor's interpretation that there are differences between placebo and active drug in time to onset of response.

The sponsor's definition of response duration is conservative because no loss of clinical benefit is allowed. However in patients with psoriasis it might be reasonable to estimate duration of response starting after the end of treatment. The relevant clinical question is what is the time interval before retreatment with a potentially toxic drug is necessary. Ideally, interpretation of duration of response should take into account the calculated clearance of alefacept. Finally, it is also more conservative to omit the addition o f 1- 2 weeks to the last observation of response.

The calculation of p=0.006 for linear dose response is not meaningful because of the nearly identical medians (89-91 days) in the alefacept groups. The duration of response in the post-treatment period using different outcome measures is not consistently superior in the alefacept groups and may be confounded by use of concomitant anti-psoriatic treatments

A conservative analysis, which does not add any days to the end of response time, and does not take into account response during the treatment period shows that the duration of response is not different between the placebo and alefacept groups (**Table 16**).

Table 16. Duration of Response (days) PGA Mild or Better

	Placebo	0.025	0.075	0.150	Diff	Linear
During follow-up					0.532	0.272
n (a)	7	16	20	17		
Median	56	77	77	75		
Min - Max	21-90	7-140	7-87	28-93		

'Diff' represents the p -value for overall treatment differences; 'Linear' represents the p -value for linear dose response.

Patient listings were examined to determine if during the post-treatment period variants of psoriasis (e.g. pustular, erythrodermic) or flares of psoriasis develop. No cases of rebound of psoriasis were identified.

Analysis of treatment failures showed a rough inverse dose-response in the proportion and severity of cases of worsening psoriasis with the highest numbers/severity in the in the placebo and low dose groups. For these analyses center 122 was excluded and LOCF was used for missing value at endpoint (See **Table 17**).

Table 17. % Change from Baseline in PASI at 2 Weeks Post Treatment

% change	placebo	0.025	0.075	0.15
≥ 75% Improvement	6 (11)	10 (19)	15 (30)	15 (28)
50-74.9 % Improvement	8 (15)	7 (13)	13 (26)	12 (23)
25-49.9 % Improvement	13 (24)	17 (33)	11 (22)	14 (26)
0-24.9 % Improvement	18 (33)	12 (23)	10 (20)	8 (15)
0.1-25% Worsening	3 (5)	3(6)	0	4 (8)
25.1–50% Worsening	2 (4)	1 (2)	0	0
50.1-75% Worsening	3 (5)	1 (2)	1 (2)	0
≥75% Worsening	2 (4)	1 (2)	0	0

Analyses of Other Secondary Efficacy Outcomes

Cross correlations between PASI score at baseline and endpoint were examined and no evidence of dose-dependent worsening of psoriasis was seen in non-responders. The patients who worsened tended to be in the placebo and low dose groups.

Patient photographs were reviewed to confirm the diagnosis of plaque psoriasis and the severity of disease at baseline and at endpoint using scaling, erythema/discoloration, area and whenever possible raised border/elevation.

Pruritus scores (using VAS 0=none 10=maximum severity) were approximately 4.5 at baseline, remained unchanged in the placebo group (-0.33) and declined by about 1.5 points in the alefacept groups.

Cross correlation between the primary efficacy outcome (static PGA with psoriasis mild or better) and the principal PASI outcome (≥ 75% improvement from baseline) showed good concordance between the two treatment outcomes for patients with PGA scores of severe, moderate-to-severe, and moderate. Nearly all these patients also failed to respond by PASI criteria. Four of 33 subjects classified as moderate (hence treatment failures) by PGA scores were considered responders by PASI scores. All the patients classified as mild, almost clear, and clear by PGA scores were also treatment successes by PASI score. There was a crude overall correlation (correlation coefficient 0.3 as calculated by sponsor) between response to treatment and lymphocyte counts (total, CD4, and CD8).

Safety

Incidence of Adverse Events

The incidence of adverse events by body system was numerically higher in the mid- and high-dose groups compared to placebo for the following systems: body-as–a-whole, digestive, nervous, metabolic, urogenital and endocrine (See **Table 18**).

Table 18. Incidence of Adverse Events by Body System

	Placebo	0.025	0.075	0.15
Number of Subjects Dosed	59 (100)	57 (100)	55 (100)	58 (100)
Subjects With ≥ 1 AE	44 (75)	45 (79)	46 (84)	44 (76)
Body as a Whole	21 (36)	31 (54)	29 (53)	27 (47)
Respiratory	25 (42)	18 (32)	17 (31)	23 (40)
Digestive	9 (15)	13 (23)	8 (15)	10 (17)
Nervous	5 (8)	9 (16)	9 (16)	12 (21)
Skin & Appendages	8 (14)	16 (28)	5 (9)	8 (14)
Musculoskeletal	6 (10)	3 (5)	8 (15)	9 (16)
Special Senses	5 (8)	4 (7)	5 (9)	3 (5)
Cardiovascular	5 (8)	3 (5)	5 (9)	3 (5)
Metabolic/Nutritional	1 (2)	3 (5)	6 (11)	1 (2)
Urogenital	1 (2)	4 (7)	1 (2)	3 (5)
Hemic & Lymphatic	2 (3)	1 (2)	1 (2)	2 (3)
Endocrine	0	0	0	1 (2)

The incidence of most common adverse events was numerically slightly higher in the active arms compared to placebo for the following: accidental injury, dizziness, flu syndrome, diarrhea, nausea, cough, myalgia, and asthenia (**Table 19**). The incidence of infectious events did not appear to be higher in the alefacept group compared to placebo for the following terms: pharyngitis, rhinitis, infection, bronchitis, otitis media, and herpes simplex. Periodontal abscess was numerically higher in the alefacept group.

Table 19. Adverse Events Occurring in ≥ 5% of Subjects by Treatment Group

	Placebo	0.025	0.075	0.15	BG9273 Total
Subjects dosed	59 (100)	57 (100)	55 (100)	58 (100)	170 (100)
Subjects with AE	44 (75)	45 (79)	46 (84)	44 (76)	135 (79)
Pharyngitis	16 (27)	10 (18)	12 (22)	15 (26)	37 (22)
Headache	8 (14)	6 (11)	9 (16)	10 (17)	25 (15)
Accidental injury	3 (5)	5 (9)	8 (15)	9 (16)	22 (13)
Rhinitis	7 (12)	5 (9)	4 (7)	7 (12)	16 (9)
Dizziness	1 2)	3 (5)	5 (9)	7 (12)	15 (9)
Flu Syndrome	3 5)	6 (11)	4 (7)	4 (7)	14 8)
Diarrhea	1 (2)	5 (9)	0	6 (10)	11 (6)
Infection	5 (8)	5 (9)	3 (5)	3 (5)	11 (6)
Nausea	0	3 (5)	3 (5)	4 (7)	10 6)
Chills	0	0	3 (5)	5 (9)	8 (5)
Cough increased	0	5 (9)	2 (4)	1 (2)	8 (5)
Myalgia	2 (3)	1 (2)	2 (4)	5 (9)	8 (5)
Rash	2 (3)	7 (12)	0	1 (2)	8 (5)
Asthenia	1 (2)	0	4 (7)	3 (5)	7 (4)
Bronchitis	2 (3)	1 (2)	2 (4)	3 (5)	6 (4)
Hypertension	3 (5)	1 (2)	3 (5)	2 (3)	6 (4)
Arthralgia	2 (3)	1 (2)	1 (2)	3 (5)	5 (3)
Herpes simplex	2 (3)	1 (2)	1 (2)	3 (5)	5 (3)
Insomnia	0	1 (2)	3 (5)	1 (2)	5 (3)
Periodontal abscess	0	3 (5)	1 (2)	1 (2)	5 (3)
Otitis media	3 (5)	0	2 (4)	0	2 (1)

Table 20 shows that there was no difference in the proportion of adverse events rated as severe across study arms. The incidence of serious adverse events was 7% in placebo and from 2 to 7% in the alefacept groups (not shown).

Table 20. Severe Adverse Events by Body System

	Placebo	0.025	0.075	0.150	Bg9273 Total
Number of subjects dosed	59 (100)	57 (100)	55 (100)	58 (100)	170 (100)
Subjects with at least one event	7 (12)	8 (14)	6 (11)	10 (17)	24 (14)
Body System					
Body as a whole	2 (3)	4 (7)	5 (9)	4 (7)	13 (8)
Respiratory	3 (5)	2 (4)	1 (2)	2 (3)	5 (3)
Skin & appendages	1 (2)	2 (4)	0	2 (3)	4 (2)
Digestive	2 (3)	1 (2)	0	2 (3)	3 (2)
Nervous	0	1 (2)	0	1 (2)	2 (1)
Cardiovascular	0	0	0	1 (2)	1 (<1)
Hemic & lymphatic	0	0	0	1 (2)	1 (<1)
Musculoskeletal	1 (2)	0	0	0	0

Laboratory data

Hematology:

Shifts in PMN, RBC, and platelets were observed; these were not dose dependent. Up to 23% of patients had shift to high PMNs. RBCs tended to shift to low in about 10% of patients. Platelet shifts were to lower or higher counts without apparent pattern.

Lymphocytes declined to low in a dose-dependent manner. The decrease in lymphocyte counts was further characterized. CD3 counts decline in a dose-dependent manner. For CD4 counts the incidence of decreases that are potentially clinically relevant (**Table 21**), the rate of decline and the duration of the decline are all dose dependent. With regard to recovery of counts, three subjects in the 0.075 mg/kg group and five in the 0.15 mg/kg group had CD4 counts lower than the lower limit of normal at the last visit. Subjects were followed until their CD4 counts rose above 300 cells/µL (LLN 320 cells/µL). The only subject whose CD4 counts did not rise within 6 weeks after the end of the study was diagnosed with metastatic testicular carcinoma, was placed on chemotherapy and radiotherapy and was withdrawn from study. While the CD4 counts increased during follow up, comparison of the difference between the baseline count and the last recorded count shows that, on average, counts had not recovered to the baseline level after treatment with alefacept.

CD8 counts showed dose-dependent pattern of incidence, rate of decline, and duration of decline similar to that seen with CD4 counts. CD8 counts increased during follow up but did not recover to pre-treatment baseline by the end of the follow up period.
There was some suggestion of slight decrease (?fluctuation) in numbers of natural killer cells (CD16-CD56) with return to baseline. B cells (CD19) did not appear to be affected.

Although there was reasonable correlation between lymphocyte counts and CD4 counts, the CI were wide (not shown) suggesting that in clinical use, CD4 counts should be monitored directly to guide alefacept dosing.

Table 21. Dose-dependent CD4+ T Lymphocyte Depletion

Treatment	N	Cell Counts			
		400	300	200	100
Placebo	(59)	12 (20)	1 (2)	0	0
0.025	(57)	15 (26)	2 (4)	0	0
0.075	(55)	26 (47)	15 (27)	3 (5)	0
0.15	(58)	40 (69)	23 (40)	6 (10)	0

Chemistry:
No evidence of hepatic, renal, endocrine/metabolic abnormalities was seen.

Anti-alefacept Antibodies:
Anti-alefacept antibodies were quantified by a comparison with normal human serum obtained from an average of approximately 20 unexposed subjects. The OD absorption considered negative was 0.1. The anti-alefacept antibody titer was the dilution at which the patient's serum achieved the cutoff.

Two subjects in the 0.15 mg/kg alefacept group tested positive: one at baseline with a titer of 5, the other on Day 162 with a titer of 5.

Skin testing for delayed hypersensitivity:
Data are shown in table14.3.28.of the License Application. To summarize the data the number of - to + shifts was subtracted from the number of + to – shifts by antigen by treatment group to obtain the net number of shifts from positive to negative (not shown). There was a suggestion of higher net number of + to – shifts in the alefacept groups compared to placebo. The data were also summarized as percentage of positive tests at baseline that shifted to negative post-treatment (see Table 22). Percentages in general were numerically higher in the alefacept group compared to placebo.

Table 22. DTH Shifts by Dose: Positive to Negative as a Percentage of Subjects Positive at Baseline.

Antigen	Dose Alefacept (mg/kg) IV			
	Placebo	0.025	0.075	0.15
Tetanus	47 (15/32)	50 (13/26)	64 (18/28)	64 (9/14)
Diphtheria	40 (4/10)	50 (3/6)	73 (8/11)	73 (8/11)
Strep	71 (5/7)	100 (3/3)	75 (3/4)	100 (5/5)
Tuberculin	78 (7/9)	100 (7/7)	86 (12/14)	82 (9/11)
Candida	60 (3/5)	75 (6/8)	88 (7/8)	75 (3/4)
Trichophyton	100 (3/3)	71 (5/7)	67 (4/6)	100 (2/2)
Proteus	36 (4/11)	53 (8/15)	46 (6/13)	69 (9/13)

Clinical Narratives of Serious Adverse Events
There were no deaths. The following serious adverse events are described in the treatment groups.
Placebo:

- Syncope, bronchitis, cholelithiasis, worsening psoriatic arthritis.

0.025 mg/kg Group:

- Worst asthma exacerbation in patient with average 1 episode /year x 10 years
- Recurrent angioedema. [See Appendix for narrative details.]
- Necrotizing facial cellulitis, patient 119006. [See Appendix, Serious Infections for narrative details.]
- Squamous cell carcinoma, skin, patient 106008 [See Appendix, Malignancies for narrative details.]

0.075 mg/kg Group:

- Elective uncomplicated cholecystectomy
- Acute syndrome with nausea vomiting and severe headache following first dosing (resolved, unexplained)
- Worsening psoriatic arthritis
- Abnormal LFTs (present at screening)

0.15 mg/kg Group:

- Testicular teratocarcinoma, patient 112-002. [See Appendix, Malignancies for narrative details.]
- Elective total knee arthroplasty
- MI long after drug clearance
- Post-surgical femoral venous thrombosis
- Borderline transient leukopenia

Reviewers' Comment
The following events in patients treated with alefacept are notable: hypersensitivity reaction, serious infection, and neoplasia.

Conclusions

Efficacy

- Approximately 20% more patients in the alefacept treated groups had a response compared to placebo.
- There was no discrimination between the two higher doses studied. Lack of difference in response between mid and high dose groups may be attributable to imbalance in baseline psoriasis severity and withholding treatment in the high dose group due to lymphopenia.
- Concomitant use of antipsoriatic therapies may have caused overestimation of the treatment effect.
- Various secondary efficacy outcomes support the primary efficacy outcome and also show evidence of treatment effect.
- Alefacept concentration quartiles do not provide additional insights into dose response.
- There was no striking difference between placebo and alefacept in time to onset of response to treatment.

Safety

- Alefacept induces dose-dependent CD2+ lymphocyte depletion (primarily CD4 and CD8).
- CD4 and CD8 counts return to within normal limits. On average, counts do not recover to the baseline level during the follow up period.
- Serious infection and neoplasms were observed, the incidence was too low for meaningful analysis. There was no evidence of opportunistic infections or reactivation of latent/chronic infections. DTH data were inconclusive.
- Rare cases of hypersensitivity reactions occurred.
- No anti-alefacept antibody development was detected.

PROTOCOL C99-711

Study Title

"A randomized, double-blind comparison of intravenous LFA3TIP versus placebo in subjects with chronic plaque psoriasis " Protocol Number:C99-711; October 21, 1999

Study Objectives

Demonstrate in subjects with chronic plaque psoriasis the efficacy and safety of LFA3TIP administered as a weekly 7.5 mg IV injection for 12 weeks by measuring the proportion of subjects with $\geq$75% reduction from baseline in PASI.

Demonstrate the efficacy and safety of LFA3TIP following two courses of LFA3TIP administered as a weekly 7.5 mg IV injection for 12 weeks per course as measured as the proportion of subjects who achieve a 75% or greater reduction from baseline in PASI.

Study Design

Phase 3, multicenter (approximately 55 sites), randomized, double-blind, parallel-group, placebo-controlled (saline), study of LFA3TIP (7.5 mg IV) in 555 subjects with chronic plaque psoriasis.

Randomization:

Subjects were randomized (centrally) in a 1:1:1 ratio to one of three cohorts. Cohort 1: two courses of LFA3TIP or Cohort 2: an initial course of LFA3TIP followed by a course of placebo or Cohort 3: an initial course of placebo followed by a course of LFA3TIP.

Stratified randomization was used with 4 strata namely 1) patients with PASI > 20 and no history of systemic therapy or phototherapy, 2) PASI > 20 and previously received systemic therapy or phototherapy, 3) PASI $\leq$ 20 and never received systemic therapy or phototherapy, 4) PASI $\leq$ 20 and previously received systemic therapy or phototherapy. A central randomization service was used.

Blinding:

Laboratory data from the central laboratory were sent directly to an independent (blinded) investigator at each site (the "laboratory assessing physician"). The laboratory assessing physician was able to change or withhold dosing with study

drug (substitution with placebo). He was instructed to not communicate any information to the other investigators, study coordinators, or the sponsor. The only unblinded person at each site was the pharmacist or designee who prepared study drug.

Open label extension study:

At the end of the second treatment course, study subjects had the option to enroll in an open-label retreatment study under a separate protocol.

Study drug

Subjects whose body weight is ≥50 kg received 7.5 mg of LFA3TIP or placebo. Subjects whose body weight is <50 kg received 5.0 mg of LFA3TIP or placebo.

Rationale for fixed dose:

In study C97-708 body weight accounted for a relatively small proportion of variation in LFA3TIP AUC over the body weight range of 60-95 kg.

Treatment course 1 and 2:

Subjects received two courses of study drug separated by a minimum of 12 weeks. Each course consisted of an IV bolus of study drug once a week for 12 weeks. Subjects were followed for 12 weeks after receiving the last dose of study drug.

Subjects were eligible to receive a second 12-week course of study drug if their plaque psoriasis severity was worse than 'clear' on Physician Global Assessment and their peripheral $CD4^+$ count was at or above 250 cells/mm^3.

Withholding treatment:

Administration of each dose of study drug was to be separated by 7 days. There had to be no clinical evidence of significant viral, bacterial, or fungal infection.

Concomitant Treatments

The sponsor provided low potency topical corticosteroids (hydrocortisone 1% cream) and emollients. If a subject discontinued study drug, systemic medications for psoriasis could be initiated only after a 4-week washout.

Study Inclusion Criteria

Subjects 16 years of age or older with chronic plaque-type psoriasis for more than 12 months with a body surface involvement of ≥10% and $CD4^+$ lymphocyte counts above the lower limit of normal were eligible.

Study Exclusion Criteria

The following were grounds for exclusion.

-Any clinically significant abnormal hematology, chemistry, or urinalysis data; erythrodermic, guttate, or generalized pustular psoriasis within 28 days.

-Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g.,

pneumonia, septicemia) within 3 months.
-Positive hepatitis C antibody or positive hepatitis B surface antigen with an ALT or AST greater than three times upper limit of normal. Positive HIV antibody.
-History of malignancy. Subjects with a history of basal cell carcinomas or fewer than 3 squamous cell carcinomas are eligible.
-Other skin disease that might interfere with psoriasis status assessments.
-Previous participation in any LFA3TIP study. Treatment with another investigational drug within 4 weeks.
-Treatment with phototherapy, systemic retinoids, systemic steroids, methotrexate, cyclosporine, azathioprine, or thioguanine within 4 weeks.
-Treatment with high potency topical corticosteroids (Class I and II) within 4 weeks or with moderate potency topical corticosteroids (Class III and IV) (other than on the scalp, palms, groin, and/or soles) within 2 weeks.
-Treatment with vitamin D analogues, topical retinoids, keratolytics or coal tar (other than on the scalp, palms, groin, and/or soles) within the 2 weeks.
-Women who were not postmenopausal for at least 1 year, surgically sterile, or willing to practice effective contraception during the study. Nursing mothers, pregnant women and women planning to become pregnant while on study.

Eligibility for Treatment Course 2

Patients had to have the following: Disease severity worse than 'clear' by Physician Global Assessment , $CD4^+$ lymphocyte count $\geq$ 250 cells/mm^3, had not received non-allowed antipsoriatic treatment before visit 8A.

Dose Modification Rules

Dosing was withheld for 2 weeks for body temperature >38^oC or clinically significant infection. The study drug was substituted with placebo if the absolute $CD4^+$ lymphocyte count from the previous week was below 250 cells/mm^3.

The study drug was permanently substituted with placebo if any subject experienced a reduction in number of absolute $CD4^+$ lymphocytes below 250 cells/mm^3 for 4 or more consecutive visits. Subjects who prematurely discontinued study drug remained in the study and continued the protocol-specified follow-up evaluations. All subjects were to be followed until their absolute $CD4^+$ lymphocyte counts returned to within normal limits.

Other reasons for discontinuation of study drug were as follows. Absolute: pregnancy; subject's choice; medical emergency. Discretionary: investigator's choice (e.g. medical reasons, non-compliance).

Primary Efficacy Endpoint

The proportion of patients with $\geq$75% improvement in PASI score at the end of the first treatment period was the primary efficacy endpoint. A standard Psoriasis Area and Severity Index was used.

Principal Secondary Efficacy Endpoint

The proportion of patients with a score of clear to almost clear by Physician Global Assessment was the principal secondary endpoint. The following 7-point scale was used: Severe, Moderate to Severe, Moderate, Mild to Moderate, Mild, Almost Clear, and Clear.

Other Secondary Efficacy Endpoints

Target Skin Lesion Assessment.

The proportion of subjects with target lesion score of 0 was assessed. The lesion was located on the trunk, ≥ 2 cm^2 , and not sun-exposed. Lesional erythema, induration (thickness), and desquamation (scaling) were graded in half-point increments from 0=none to 4= very marked.

Quality of Life.

Health-related quality of life (QOL) was evaluated in this study using three standard scales, namely the SF-3 Health Survey (SF-36), the Dermatology Life Quality Index (DLQI), the Dermatology Quality of Life Scales (DQOLS). A four-item Treatment Convenience Scale developed by the sponsor was also used.

The SF-36 evaluates health status in eight areas: physical functioning, limitations due to physical problems, bodily pain, general health, vitality, social function, limitations due to emotional problems, and mental health. The SF-36 has been used in studies of psoriasis. SF-36 scale scores range from 0 (worst) to 100 (best).

The DLQI is a ten-item questionnaire designed to evaluate QOL of patients with a variety of skin conditions, including psoriasis. It addresses daily activities, leisure activities, impact on work or school, personal relationships, symptoms and feelings, and treatment-related distress. The Overall DLQI scale score ranges from 0 (best) to 30 (worst).

The DQOLS contains 29 items that represent eight categories: embarrassment, despair, irritability, distress, everyday activities, summer activities, social activities, and sexual activity. The DQOLS also includes 12 symptoms (redness, itch, scarring, flaking, rawness, change in skin color, pain, tiredness, swelling, bleeding, aching, and burning). The DQOLS scale scores range from 0 (best) to 100 (worst).

The Treatment Convenience scale looks at the impact of treatment on patients' daily activities, the time spent managing their psoriasis, the discomfort due to treatment, and patients' overall rating of the convenience or inconvenience of their treatment. The Treatment Convenience scale score ranges from 0 (worst) to 100 (best).

Clinical and Laboratory Assessments:

The schedule for Treatment Courses 1 and 2 was as follows.

- Weekly dosing visits: (Visits 1A-12A); (Visits 1B-12B).
- Follow-up visits: (Visits 13A-17A); (Visits 13B-17B).
- Monthly interim visit(s): After the first treatment course patients had monthly visits.

Assessment of Efficacy and PK:

The following were measured: PASI; Physician Global Assessment; target lesion assessment; body surface photography; quality of life assessment. LFA3TIP serum concentrations.

Assessment of Safety:
The following were performed: physical examinations; monitoring for adverse events; monitoring for infections; blood chemistry, hematology, lymphocyte subset analyses; urinalysis; antibodies to LFA3TIP. Peripheral lymphocyte subset quantification using flow cytometric analysis ($CD3^+$, $CD4^+$, $CD8^+$, and $CD19^+$). Antibodies to LFA3TIP. Monitoring for infections. Monitoring for adverse events. Adverse events were defined as any sign, symptom, data or medical diagnosis, regardless of relationship to study drug, that began or worsened after the start of study drug treatment. Adverse events were recorded in the subject's adverse event CRF. Definitions of seriousness, severity and causality were included in the protocol. Provisions were made for reporting serious adverse events to sponsor, to IRB, and to FDA.

Assessment Responsibilities Treatment and Follow Period:
The examining physician performed the following: physical examination including measurement of vital signs; photography; Physician Global Assessment of efficacy; PASI; assessment of target skin lesion; assessment of any new or ongoing viral, bacterial, or fungal infections. The Laboratory Assessing Physician evaluated all lab data and in particular hematology and analysis of peripheral lymphocyte subsets.

Statistical Analysis Plan

Sample size considerations:

The sponsor assumed that at endpoint the proportion of responders (≥75% improvement in PASI after the first treatment) would be 25% in the active group and 10% in the placebo group. A sample size of 370 subjects (2 active:1 placebo) would have 95% power and a type I error rate of 5% to show efficacy.

However to achieve sufficient power for important secondary endpoints (e.g. to demonstrate the efficacy of retreatment with LFA3TIP) additional subject accrual would be needed. The sponsor assumed that 50% of subjects would clear, withdraw, or fail to achieve CD4 counts above 250 between the two dosing periods, therefore the study required an additional 185 subjects for a total accrual of 555 subjects.

Missing data:
The method of last value carried forward was initially proposed for missing response endpoints except for analyses of duration of response, summation of response, and time to response. Subjects who discontinued study medication and/or used non-allowed therapies were to be evaluated using the last endpoint measured. The duration of response endpoint would be truncated 12 weeks after the last retreatment injection of study drug. Subjects in response at the end of the study had 14 days added for the duration of response. The sponsor drew a straight line between the last visit when patient was in response and the following visit where loss of response occurred. The cut point

was calculated using the time when the straight line cross the horizontal response line (e.g., 75% PASI). The interval between two cut points defined the duration.

Baseline Data:

Data were summarized for each treatment group. Study centers were pooled by geographic regions. Subjects were stratified by baseline PASI and prior systemic therapy into four strata.

Efficacy Analyses:

All tests were two-sided and were considered statistically significant at the 5% level. Confirmatory analyses were based on an intent-to-treat population defined as patients randomized, receiving at least one dose of study drug, and having at least one post-treatment efficacy assessment. Binary outcomes were modeled by logistic regression, continuous responses by analysis of variance or covariance, and time to event responses by a Cox proportional hazards model. The model included terms for geographic region, strata, and treatment. The interactions of treatment group and geographic region, plus treatment group and strata, was tested and included in the model if significant at the 5% level.

Primary Efficacy Analysis:

The proportion of subjects with a reduction in PASI of at least 75% from baseline without the use of other systemic therapies was evaluated at Visit 13A (Day 92) using logistic regression with the general model described above. The comparison was between active (cohorts 1 and 2) versus placebo (cohort 3) treatment arms. Additional covariates including baseline PASI, gender, race, age, body surface area, and baseline weight were tested.

Secondary Efficacy Analyses. First Treatment:

The proportion of subjects who achieved a Physician Global Assessment of 'almost clear' or 'clear' at Visit 13A (Day 92) without the use of phototherapy or other systemic therapy was evaluated with logistic regression using the general analysis model. The comparison was between active (cohorts 1 and 2) versus placebo (cohort 3).

The overall DLQI scale score were analyzed by ANCOVA using the general analysis model and including baseline DLQI score. The interaction between treatment and baseline DLQI score additionally was tested and included in the model if significant at the 5% level.

Secondary Efficacy Analyses. Retreatment:

The proportion of subjects with a reduction in PASI of at least 75% from baseline (Visit 1A) without the use of phototherapy or other systemic therapy was evaluated at Visit 13B with logistic regression using the general analysis model. The comparison was between subjects who received 12 weeks of active therapy retreatment (cohort 1) and 12 weeks of placebo retreatment (cohort 2). Subjects with a Physician Global Assessment of 'clear' at the end of the follow-up after the

first course of treatment (Visit 17A) were not included in this analysis if their disease did not worsen and they did not receive retreatment during the study.

The proportion of subjects who achieved a Physician Global Assessment of 'almost clear' or 'clear' at 2 weeks after the last retreatment dose (Visit 13B) without the use of phototherapy or other systemic therapy was evaluated with logistic regression using the general analysis model. The comparison was between subjects who received 12 weeks of active therapy retreatment (cohort 1) and 12 weeks of placebo retreatment (cohort 2). Subjects with a Physician Global Assessment of 'clear' at the end of follow-up after the first course of treatment were not included in this analysis if their disease did not worsen and they did not receive retreatment during the study.

The proportion of subjects whose PASI at 2 weeks post retreatment (Visit 13B) was less than their PASI at 2 weeks post the first treatment (Visit 13A) were compared between subjects receiving 12 weeks of active retreatment (cohort 1) versus those with 12 weeks of placebo retreatment (cohort 2). This analysis was performed with logistic regression using the general analysis model.

<u>Additional Secondary ("Tertiary") Efficacy Analyses:</u>

- Target Skin Lesion.
  The proportion of subjects with induration of 0 in the target lesion at Visits 13A were compared between active (cohorts 1 and 2) versus placebo (cohort 3) arms using logistic regression and the general analysis model.

- 50% Improvement in PASI. First Treatment.
  The proportion of subjects (placebo versus active treatment groups) with a reduction in PASI of at least 50% from baseline at Visit 13A evaluated with logistic regression and the general analysis model.

- 50% Improvement in PASI. Retreatment.
  The proportion of subjects with a reduction in PASI of at least 50% from baseline at 2 weeks after the last retreatment dose (Visit 13B) were evaluated with logistic regression using the general analysis model. The comparison was between subjects who received 12 weeks of active therapy retreatment (cohort 1) and 12 weeks of placebo retreatment (cohort 2). Subjects with a Physician Global Assessment of 'clear' at the end of follow-up after the first course of treatment were included in this analysis if their disease did not worsen and they did not receive retreatment during the study.

- Percentage Change in PASI.
  PASI scores and percentage change from baseline in PASI scores were analyzed at each psoriasis assessment visit with ANOVA or ANCOVA.

- Quality of Life.

SF-36, DQOLS scale, and Treatment Convenience scores were analyzed by ANCOVA using the general analysis model and including baseline QOL score. The interaction between treatment and baseline QOL score was tested and included in the model if significant at the 5% level.

- Summation of Response during Treatment, Retreatment, and Follow-up.
  Summation of response for each of the response definitions (PASI 75% below baseline, PGA of 'almost clear' or 'clear', and PASI 50% below baseline) was evaluated with ANOVA using the general analysis model. Only subjects who responded to treatment were included in the analysis. The summation of response was calculated as days between the first visit at which response was achieved and the next visit they were assessed as either a non-responder, the subject withdrew, or the subject reached the end of the study, whichever came first. The summation of response endpoint was truncated at the end of the study. Subjects who were in response at study end had 14 days added for the summation of response. The comparison for summation of response was between subjects receiving 12 weeks of active retreatment (cohort 1) versus those with 12 weeks of placebo retreatment (cohort 2).

- Duration of Response.
  Duration of response for each of three definitions was evaluated with summary statistics. Only subjects who responded to treatment were included in the analysis. The duration of response was calculated after the last dose as days between the first visit at which response was achieved and the next visit when patients were assessed as either a non-responder, they withdrew, or reached the end of the study, whichever came first. The duration of response endpoint was truncated at the end of the study. Subjects who were in response at study end had 14 days added for the duration of response. The duration of response was assessed for subjects who were first treated with active drug and retreated with placebo (cohort 2) as well as the subset of subjects on cohort 1 achieving and maintaining a Physician Global Assessment of 'clear'.

- Onset of Clinical Response.
  Time of onset (time from baseline to first occurrence of response) based on the endpoint of PASI 75% below baseline and PGA of 'clear' or 'almost clear' was analyzed using Cox Proportional Hazards using the general analysis model. Time-to-event curves were plotted using the Kaplan-Meier method. Subjects who withdrew or did not respond by their last visit or the end of the study were censored. This analysis was performed for both the treatment and the retreatment courses. Comparison for the first course of treatment was between active (cohorts 1 and 2) and placebo (cohort 3). Comparison for retreatment was between active (cohort 1) and placebo (cohort 2).

Safety Analyses

Any subject who received one dose of study drug and had post baseline data was considered evaluable for tolerability/safety analyses. The incidence of adverse events was

tabulated by treatment group, severity, and relationship to treatment. The incidence of infections and signs, symptoms, or events associated with infection was presented by treatment group. For laboratory data shift tables described changes from low, normal, or high. The effect of LFA3TIP on lymphocytes and lymphocyte subsets was examined by calculating the rates of change in subsets over time. The duration that lymphocytes and lymphocyte subsets were below several thresholds was also evaluated.

Study Monitoring

A CRO ---------- was responsible for study initiation, monitoring, management of adverse event reports, and data management, analysis of all hematology, blood chemistry, and urine samples. ---------- acted as the central randomization service for this study. A blinded sponsor's committee met to monitor subject accrual, non-compliance, and to consider modifications of the protocol. The committee members were Biogen's medical director, program manager, clinical project manager, and project statistician, two study coordinating investigators, and two study principal investigators.

Reviewers' comments

The phase 3 protocol outlined above is designated Version 1 and was the outcome of a series of discussions between the agency and the firm. The agency and the firm reached agreement on the final version (Version 2) of the phase 3 protocol at a teleconference on November 24, 1999. The firm sent to the agency the final revised phase 3 protocol on January 22, 2000. The protocol contained the following modifications and clarifications.

- *Patients must have had CD4 counts at or above the lower limit of normal to receive a second course of treatment.*
- *At the end of the study, subjects were followed until they reached a lymphocyte count of 75% of the original baseline value. At that point lymphocyte subsets would be quantified.*
- *Subjects with missing efficacy data at endpoint were considered treatment failures in the primary efficacy analysis*
- *The primary efficacy analysis was performed on the intent to treat population.*
- *The only covariates used in the primary efficacy analysis were the four stratification criteria and the center's geographic region.*
- *The geographic region was prospectively defined by dividing the US into 4 quarters by latitude and longitude with roughly the same number of study centers in each quarter.*
- *The secondary efficacy endpoints in order of priority were as follows:*
    - *Proportion of subjects with PGA of "clear or almost clear" after 1st treatment*
    - *Proportion of subjects with $\geq$75% improvement in PASI after 2nd treatment*
    - *Proportion with PGA of "clear or almost clear" after 2nd treatment*
    - *Proportion with PASI lower after 1st treatment than after 2nd treatment*
    - *Changes in QOL as measured by DLQI*
- *Standard definitions for grading PGA using a "static" assessment were added.*

In addition the sponsor agreed to conduct additional studies in a small number of subjects to characterize the effects of LFA3TIP on immune function including primary

and secondary antibody responses to neoantigens, T-cell proliferative responses and cytokine production in response to antigens.

With these modifications the phase 3 study was judged to be well designed and adequately controlled for the purpose of demonstrating the efficacy and safety of LFA3TIP administered as a weekly 7.5 mg intravenous bolus for 12 weeks to patients with plaque psoriasis.

The study was also designed to provide information on other clinically important questions including the proportion of subjects with complete responses to treatment, the time of onset of the response to treatment, the duration of the response after the end of treatment, the safety and efficacy of retreatment.

Major Protocol Amendments

Amendment 1 dated 01-11-00:
The agreed-upon changes (see above) were added to the protocol.

Amendment 2 dated 11-12-00:
The option to receive open label retreatment was withheld until more clinical data became available.

Study Results

Patient Disposition, Demographics and Baseline Disease Characteristics

Discontinued Subjects (Section 16.2.1)
In the cohort never dosed one patient (137206) is listed; he developed atrial fibrillation before randomization. Review of reasons for discontinuations indicates that the principal reasons were lack of improvement or worsening of disease, scheduling conflicts, protocol deviations, and loss to follow up.

Patient disposition
A high proportion of patients entered into the second treatment period at the end of the scheduled follow up period. The criteria for the second treatment were: psoriasis less than clear by PGA, normal lymphocyte count, and no usage of proscribed anti-psoriatic medication. In the two patient disposition tables the following are grouped together under the category adverse event: 1)adverse event, 2)intolerance to drug, 3) laboratory abnormality.

Course 1
Sixty-three (11%) of the 553 patients dosed did not complete the 12-week treatment period (**Table 23**). The percentages of patients not completing the 12-week treatment period in Course 1 were 17 and 8% for the placebo and combined alefacept groups, respectively. The most common reason for not completing the 12-week treatment period in Course 1 was patient decision (5%). More patients in Cohort 3 (placebo/alefacept) discontinued for this reason (10%) than in the other two cohorts who received alefacept in Course 1 (3% in each). Thirty-nine patients (7%) withdrew from the study during the dosing period, the greatest number (10%) being in Cohort 3 (placebo/alefacept) By study

drug, the rates of withdrawal were 10 and 6% for the placebo and combined alefacept groups, respectively. The most commonly reported reason for withdrawal was patient decision with a slightly higher rate in those who received placebo (placebo vs. combined alefacept: 5 *vs.* 2%).

Course 2
The proportion of non-completion/withdrawal was higher in the control group. The percentages of patients not completing the 12-week treatment period in Course 2 were 3, 13, and 6% for Cohorts 1 (alefacept/alefacept), 2 (alefacept/placebo), and 3 (placebo/alefacept), respectively. The most common reasons for discontinuation of treatment were patient request (3%) and other (2%).

The rates of withdrawal from the study during the treatment period in Course 2 were 3, 12, and 5% for Cohorts 1 (alefacept/alefacept), 2 (alefacept/placebo), and 3 (placebo/alefacept), respectively (**Table 24**). The most commonly reported reasons for withdrawal from the study during the treatment period were "other" (3%) and patient request (2%).

Table 23. Patient Disposition Treatment Course 1

	Cohort 1	Cohort 2	Cohort 3
RANDOMIZED	187	187	188
COURSE 1: DOSED	183 (100)	184 (100)	186 (100)
COMPLETED TREATMENT	172 (94)	164 (89)	154 (83)
Discontinued Treatment	11 (6)	20 (11)	32 (17)
-Loss to Follow-up	1 (<1)	2 (1)	6 (3)
-Adverse Event	1 (<1)	6 (3)	1 (<1)
-Laboratory Abnormality	0	0	0
-Worsening Disease	2 (1)	6 (3)	5 (3)
-Subject Request/Voluntary	5 (3)	5 (3)	19 (10)
-Other	2 (1)	1 (<1)	1 (<1)
Withdrawn during Treatment	8 (4)	13 (7)	18 (10)
-Loss to Follow-up	1 (<1)	1 (<1)	5 (3)
-Adverse Event	1 (<1)	3 (2)	0
-Worsening of Disease	2 (1)	3 (2)	1 (<1)
-Subject Request/Voluntary	3 (2)	4 (2)	9 (5)
-Other	1 (<1)	2 (1)	3 (2)
Withdrawn during F/U	8 (4)	13 (7)	11 (6)
COMPLETED FOLLOW UP	167 (91)	158 (86)	157 (84)

Table 24. Patient Disposition Treatment Course 2

	Cohort 1	Cohort 2	Cohort 3
COURSE 2: ENTERED	167	158	157
Withdrawn before Treatment	13	16	4
-Adverse Event	1	1	0
-Worsening Disease	0	1	0
-Subject Request	1	2	1
-Other	11	12	3
DOSED	154 (100)	142 (100)	153 (100)
COMPLETED TREATMENT	149 (97)	124 (87)	144 (94)
Discontinued Treatment	5 (3)	18 (13)	9 (6)
-Loss to Follow-up	1 (<1)	1 (<1)	3 (2)
-Adverse Event	0	1 <1)	1 (<1)
-Worsening Disease	1 (<1)	2 (1)	0
-Subject Request	2 (1)	8 (6)	2 (1)
-Other	1 (<1)	6 (4)	3 (2)
Withdrawn during Treatment	4 (3)	17 (12)	7 (5)
-Loss to Follow-up	1 (<1)	1 (<1)	2 (1)
-Subject Request/Voluntary	1 (<1)	9 (6)	1 (<1)
-Other	2 (1)	7 (5)	4 (3)
Withdrawn during Follow-up	7 (5)	7 (5)	6 (4)
COMPLETED FOLLOW-UP	143 (93)	118 (83)	140 (92)
COMPLETED COURSE 1 AND COURSE 2	149(81)	124 (67)	144 (77)

Demographics

Demographic variables at baseline were well balanced across groups (**Table 25**). Median age was 44; nine patients (2%) were between ages 16-20 years and 79 patients (14%) were of age 60 years or greater. Median weight was 90 kg. Study patients were mostly men (70%) of Caucasian origin (90%).

Table 25. Demographic Data

		COHORT 1 (N=183)	COHORT 2 (N=184)	COHORT 3 (N=186)
AGE (yrs):	median (min-max)	45 (16–84)	44 (18–77)	44 (18-76)
BODY WEIGHT (kg):	median (min-max)	90 (49-163)	92 (46 –206)	91 (54- 170)
GENDER:	women	52 (28)	55 (30)	59 (32)
	men	131 (72)	129 (70)	127 (68)
ETHNIC GROUP:	Caucasian	165 (90)	167 (91)	162 (87)
	Black	4 (2)	5 (3)	8 (4)
	Asian	3 (2)	2 (1)	1 (<1)
	Hispanic	5 (3)	8 (4)	11 (6)
	other	6 (3)	2 (1)	4 (2)

Disease Characteristics at Baseline

By a variety of criteria it is clear that nearly all study patients can be classified as having moderate to severe disease. All patients had chronic disease (median duration nearly 20 years), all had ≥10% BSA involvement, and nearly 80% had history of major anti-psoriatic treatment (**Table 26**). By PGA only 7% of patients had less than moderately severe disease.

Table 26. Disease Severity at Baseline

		COHORT 1	COHORT 2	COHORT 3
Disease Duration (yrs):	median (min-max)	18 (3-54)	20 (2-60)	17 (2-55)
PASI:	median (min-max)	15 (4-51)	15 (4-56)	15 (4-56)
BSA involvement (%):	median (min-max)	22 (10-98)	22 (10-95)	22 (10-85)
Major Anti-psoriatic Treatment:	N (%)	141 (77%)	141 (77%)	147 (79%)
PGA ≥ moderately severe:	N (%)	181 (94%)	181(93%)	175(93%)

As judged by the patients based on a 3-point scale, the proportion of patients who failed (unchanged or worsened) a specific major anti-psoriatic therapy ranged from about 20 to 50% (**Table 27**).

Table 27. Response to Previous Major Anti-psoriatic Treatment

		COHORT 1 (N=183)	COHORT 2 (N=184)	COHORT 3 (N=186)
METHOTREXATE	Worsened	4/ 64 (6)	2/ 69 (3)	1/ 55 (2)
	No Change	21/ 64 (33)	21/ 69 (30)	16/ 55 (29)
	Improved	39/ 64 (61)	46/ 69 (67)	38/ 55 (69)
CYCLOSPORIN	Worsened	0/ 22	2/ 23 (9)	0/ 14
	No Change	5/ 22 (23)	5/ 23 (22)	4/ 14 (29)
	Improved	17/ 22 (77)	16/ 23 (70)	10/ 14 (71)
RETINOIDS	Worsened	2/ 32 (6)	3/ 32 (9)	2/ 28 (7)
	No Change	15/ 32 (47)	13/ 32 (41)	12/ 28 (43)
	Improved	15/ 32 (47)	17/ 32 (53)	14/ 28 (50)
PUVA	Worsened	3/ 61 (5)	2/ 70 (3)	2/ 56 (4)
	No Change	23/ 61 (38)	20/ 70 (29)	18/ 56 (32)
	Improved	36/ 61 (59)	48/ 70 (69)	36/ 56 (64)
UVB	Worsened	6/ 89 (7)	8/ 89 (9)	8/101 (8)
	No Change	31/ 89 (35)	32/ 89 (36)	39/101 (39)
	Improved	52/ 89 (58)	49/ 89 (55)	54/101 (53)

STUDY CONDUCT

Study Centers

51 principal investigators participated in the trial. All the principal investigators had experience with clinical trials and with few exceptions they were board-certified dermatologists. At every center the examining physicians were qualified dermatologists. A contract research organization ---------- managed most aspects of the trial including clinical laboratory measurements.

For quality assurance purposes a ---------- audited the following components at 13 study centers during the course of the trial:

- Investigator file and project management file at Biogen and ---------- GCP documentation in the Investigator's files at the site
- All informed consent and serious adverse event documentation
- Source documents and CRF for a sample of subjects

The record contains audit certificates for each of the 13 centers. There is no information on what the audits showed.

Randomization Codes (Section 16.1.7)

Nine subjects are listed in the cohort "never dosed". Presumably these patients were randomized but the treatment allocation is not given.

Two formulations of BG9273 are listed: ---------- and Biogen (Cambridge). The first treatment course used the -------- formulation exclusively. The second treatment course used either the -------- or the Cambridge formulations.

Adequacy of the blind

The FDA inspector confirmed the identity, qualifications and procedures used by: Laboratory Assessing Physician (evaluates and maintains lab data, communicates changes in study drug treatment to the pharmacist, may communicate with Examining Physician if required by patient safety), and by Pharmacist (unblinded, maintains randomization log). The inspector also determined if other study personnel or monitors had access to information maintained by laboratory assessment physician and by pharmacist.

Protocol Deviations

The incidence of protocol deviations was not strikingly different among study centers. A few patients were not stratified correctly due to errors in history of previous systemic treatments obtained at screening; this did not affect the efficacy outcome. Other common deviations were in the following categories: study visits outside specified window, omission of portions of physical examination (e.g. genitalia), clinical laboratory, study drug administration, admission criteria, and other medication. The use of other medications was further examined. During the course of the study a number of patients received potent anti-psoriatic treatments. The principal reasons were worsening of psoriasis, lack of response to study treatment, presence of psoriasis variant (e.g. psoriatic arthritis), insufficient wash-out of antipsoriatic therapy. **Table 28** shows the rationale for use of various antipsoriatic therapies. Lack of improvement/worsening of psoriasis was the most common reason for starting antipsoriatic treatment.

Table 28. Use of Antipsoriatic Therapies by Study Patients

Patient #	cohort	course	day	event	Treatment
116205	1	2	93 121	-- flare 78% BSA	temovate cyclosporine
124202	1	1	3-9	withdrawn	cyclosporin, temovate
129202	1	1	107	--	methotrexate
129209	1	1	94	High severity psoriasis	Cyclosporin x 5 weeks
130203	1	1	90	Poison ivy	prednisone
135211	1	1	67	sunburn	UV (sunlight)
132201	1	1 2	120 106-134	-- worsening psoriasis	Kenalog sc in plaques Kenalog SC, UVB
142205	1	2	107 120	severe psoriasis flare	Targretin, prednisone
142206	1	2	92 120 134	psoriasis flare pustular psoriasis flare severe psoriasis guttate flare	Targretin triamcinolone .01% UVB narrow band
142210	1	2	134	severe psoriasis	trimacinolone 0.1%
154206	1	1 2	150 116	-- lack of improvement	PUVA methotrexate
154207	1	1	120	--	Kenalog, ultravaite
154209	1	1	87	Lack of improvement	ultravaite
161208	1	1	163	--	Prednisone,diprotene
201201	1	2	1	--	Bethametasone valerate
201207	1	1 2	103 106	-- --	UV (tanning salon) Moderate potency steroid
205209	1	1	78	Lack of improvement	Metothrexate, cyclosporin
205212	1	1 2	106 109	-- --	UVB Elocom
206209	1	1	157	Worsening psoriasis	prednisone
103207	2	1	78	Psoriatic arthritis	Systemic steroids methotrexate
106206	2	2	106	--	methotrexate
129210	2	2	158	Lack of improvement	cyclosporin
129211	2	1	69		UV (sun), face forearms
129212	2	2	77 119	Painful psoriasis plaques	Elocon diproline
135204	2	1	18	Herpes zoster	prednisone
137201	2	2 2	99 135	Flaring of psoriasis “”	Dovonex, diprolene tazovac
137203	2	2	121	flaring	TAC Eucerin
137204	2	2	92 144	Flaring of psoriasis extensive flaring	TAC Eucerin ---
137211	2	1	1	Inadequate washout	Systemic retinoid
138201	2	2	-63 (pre 2nd treatment)		Cyclosporin, dovonex, temovate
142203	2	2	92-134	Severe psoriasis flare	Soriatane, prednisone, temovate, UVB
142204	2	1	106-176	Psoriatic arthritis	Methotrexate, kenalog IM
142207	2	2	106	Worsening psoriasis	Targretin, temovate, dovonex

142211	2	1 2	134 interim visit	Psoriasis flare --	Methotrexate metothrexate
142213	2	2	78 134	Inflamed plaques Severe psoriasis	Triamcinolone UVB
144203	2	2	131	Painful lesions	Embeline E CR
149209	2	1	92 120		Psorcon E Ultravate
153203	2	1	135	Skin discomfort	Triamcinolone 0.1%
154212	2	2	43	Psoriasis exacerbation	elocon
160209	2	2	79	--	temovate
205202	2	2	88	--	UV (tanning salon)
205211	2	1	92	--	Dovonex diprososne
210205	2	2	92	--	UVB
210206	2	2	121	Treatment of psoriasis	UVB, bethamethasone
210207	2	2	106	Treatment of psoriasis	Acitretin, halcinonide
106210	3	1	9	Worsening psoriasis	triamcinolone
108208	3	1	16	Flaring psoriasis	cyclosporin
110202	3	2	149	psoriasis	thioquanine
114210	3	1	-27	Palmar plaques	temovate
116203	3	2	153	“Upper respiratory infection”	prednisone
127206	3	2	162	psoriasis	cyclosporin
129201	3	2	106	--	cyclosporin
135205	3	1	70	sunburn	UV (sunlight)
136204	3	2	83 (Post-discontinuation)	<4 weeks washout of study drug	metothrexate
136210	3	2	-260		UVB
137207	3	2 2 2	88 129 142	Psoriatic arthritis “ scalp lesions	Medrol dose pack Cortisone injection Dovonex clobetasol
137208	3	1	134	Severity of psoriasis	cyclosporin
137209	3	1 2	48 106	Flare Worsening psoriasis	None listed Psoriatane, UVB, triamcnl
137212	3	2 2	1 49	-- --	TAC Eucerin UVB
137213	3	2	92	Flaring psoriasis	Dovonex, clobetasol
142202	3	1 1 2 2	59 107 107 134	Psoriatic arthritis “ “ "	Prednisone methotrexate methotrexate prednisone
142215	3	1 2	110 135	Psoriasis Severe psoriasis	Methotrexate psoriatane
144201	3	1	102	--	temovate
145205	3	1 2	156 107	Back pain --	Cortisone injection Ultravate, tazorac
146201	3	2	60	Occipital neuralgia	depomedrol
146202	3	1	45	Sunburn	UV (not coded as non-allowed therapy)
149204	3	1 1	106 134	-- --	Psorcon Temovate
156201	3	1	134	--	diprolene
160204	3	1	57	Lack of improvement	Ultravate, triamcinolone
201202	3	1	70	--	betamethasone
201204	3	1	10	Sun tanning	UV

201210	3	1	169	--	methotrexate
201212	3	2	-7	Sun tanning	UV
201214	3	2	137	Sun tanning	UV
205203	3	1	77	Lack of response	dovonex
205205	3	1	106	--	elecom
205206	3	1 1	56 77	-- Lack of response	Diprosone, dovonex cyclosporin
210201	3	1	69	--	UVB
210202	3	2	106	--	Calcipotriol

Reviewers' comments:
Use of concomitant antipsoriatic treatment during course 1 and in the interval between course 1 and 2 argues for using PASI score at visit 1B (instead of 1A) as baseline for assessment of response to course 2.

Table 29 shows the proportion of patients using concomitant antipsoriatic therapy by specific treatment and by dose group. The majority of patients used emollients and low potency corticosteroids.

Reviewers' comment: The sponsor has stated that they analyzed the use of concomitant therapy as follows. The patients who were classified as responders and who had used systemic treatments such as the ones listed in the table below or who had used potent topical steroids or retinoids, regardless of the indication, were reclassified as non-reponders based on the use of disallowed therapies.

Because mid-potency topical steroids were allowed in certain areas of the body, but not others, the sponsor states that they reviewed the patients' charts to determine who had used these medicines in disallowed areas. Subsequently, those patients who had used these medications on disallowed sites were then counted as non-responders. The agency cannot easily confirm how this was actually done. However, the use of mid-potency steroids was somewhathigher in the placebo group than in the alefacept group.

Table 29. Concomitant Antipsoriatic Therapies-c99 711

	PLACEBO	ALEFACEPT 7.5 mg	TOTAL
Patients dosed in course 1	186 (100)	367 (100)	553 (100)
Patients receiving concomitant medication in Course 1-during treatment period	168 (90)	347 (95)	515 (93)
Systemic therapy and Phototherapy	6 (3)	10 (3)	16 (3)
Prednisone	2 (1)	5 (1)	7 (1)
Cyclosporin	1 (<1)	1 (<1)	2 (<1)
Methylprednisolone	0	1 (<1)	1 (<1)
Methotrexate	0	0	0
Gold	0	1 (<1)	1 (<1)
UV light therapy	1 (<1)	0	1 (<1)
Prednisolone acetate	1 (<1)	1 (<1)	2 (<1)
Prednisolone	0	0	0
Dexamethasone	1 (<1)	1 (<1)	2 (<1)
Potent/ Superpotent Topical	4 (2)	16 (4)	20 (4)

Steroids			
Clobetasol Proprionate	2 (1)	7 (2)	9 (2)
Ulobetasol Proprionate	0	4 (1)	4 (<1)
Betamethasone Dipropionate	1 (<1)	2 (<1)	3 (<1)
Diflorasone diacetate	0	2 (<1)	2 (<1)
Fluocinonide	0	1 (<1)	1 (<1)
Clobetasol	1 (<1)	0	1 (<1)
Mid-potency Topical Steroids	36 (19)	45 (12)	81 (15)
Betamethasone valerate	8 (4)	6 (2)	14 (3)
Fluticasone proprionate	6 (3)	12 (3)	18 (3)
Prednicarbamate	2 (1)	0	2 (<1)
Mometasone fuorate	4 (2)	4 (1)	8 (1)
Betamethasone	1 (<1)	2 (<1)	3
Triamcinolone	8 (4)	12 (3)	20
Triamcinolone acetonide	4 (2)	5 (1)	9
Hydrocortisone valerate	2 (1)	2 (<1)	4
Hydrocortisone butyrate	1 (<1)	2 (<1)	3
Low-potency topical steroids	114 (61)	206 (56)	320 (58)
Corticosteroids/Dermatological Preparations	0	1 (<1)	1 (<1)
Desocort	0	1 (<1)	1 (<1)
Hydrocortisone	104 (56)	187 (51)	291 (53)
Fluocinolone acetonide	4 (2)	8 (2)	12 (2)
Desonide	4 (2)	6 (2)	10 (2)
Cortisone acetate	0	3 (<1)	3 (<1)
Cortisone	0	0	0
Hydrocortisone acetate	1 (1)	0	1
Alclometasone dipropionate	1 (1)	0	1
Non-steroidal topical therapies	7 (4)	16 (4)	22 (4)
Calcipotriol	4 (2)	6 (2)	10 (2)
Coal tar	2 (1)	8 (2)	10 (2)
Coal tar solution	1 (<1)	1 (<1)	2 (<1)
Salicylic acid preparations	0	1 (<1)	1 (<1)

The following patients were excluded from the efficacy analyses.

Table 30. Patients excluded from efficacy analysis

Patient Number	Investigator	Study Site
112-210	Sherer	New York
116-204	Menter	Dallas
123-210	Savin	New Haven
128-201	Hampel	New Braunfels (TX)
131-205	Cognetta	Tallahassee
136-201	Goffe	Seattle
137-206	Gordon	Chicago
156-201	Aton	Martinez (GA)
156-202	Aton	Martinez
156-203	Aton	Martinez
156-204	Aton	Martinez
156-205	Aton	Martinez
156-206	Aton	Martinez
156-207	Aton	Martinez
160-202	Hahn	Indianapolis
201-205	Bissonnette	Montreal

Study Drug Accountability

This section was reviewed to identify patients who underwent changes in study treatment due to safety issues. The following patients were notable for persistent decrease in CD4 counts occurring during alefacept treatment or for discontinuation of alefacept due to adverse event.

123205 (cohort 1, course 1) permanent placebo substitution due to persistently low CD4, after visit 5
104201 (cohort 2, course1) permanent placebo substitution due to persistently low CD4
105201 (cohort 2, course2) received alefacept on visit 1B by mistake.
123209 (cohort 2, course 1) permanent placebo substitution due to persistently low CD4, concomitant clinically significant infection.
134201 (cohort 2, course 1) permanent placebo substitution due to persistently low CD4
135206 (cohort 2, course 1) study treatment stopped, prednisone started for temporal arteritis
139202 (cohort 2, course 1) permanent placebo substitution due to persistently low CD4
150208(cohort 2, course 1) permanent placebo substitution due to persistently low CD4
131202(cohort 3, course 2) permanent placebo substitution after visit 6 due to ??error
145215 (cohort 3, course 2) persistently low CD4 visit 9-12
201202(cohort 3, course 2) visit 9 SAE episcleritis, study treatment discontinued

PK data

Examination of PK data (drug concentration over time) showed that in all three study groups some of the measurements may have been erroneous. For example from visit 1A to 17A approximately seven percent of patients in the placebo/alefacept group had measurable concentration of alefacept at a time when they were to have received placebo. This observation was unexplained and was taken as an unfavorable indication of the quality of the study conduct.

The sponsor is currently evaluating this anomaly. They have obtained evidence that at least some of these patients' serum contains a factor that interferes with the assay used to measure alefacept and yields false positive results.

Case Report Forms

Baseline: History of previous antipsoriatic therapy

The screening visit captured response to previous psoriatic treatments on a 3-point scale (worse, improved, unchanged). Duration of treatment and date of the last treatment were also recorded.

In-treatment visit. Clinical assessments before administration of study drug:
At each visit during the treatment periods the CRF listed all the required testing and assessments. At a minimum the following were required.

Visit 10A

The following tests and evaluations should be performed at this visit prior to administration of study drug:

- Concomitant Therapies
- Adverse Events
- Hematology
- Lymphocyte Subset Analysis
- New or Ongoing Infection Assessment
- Study Drug Administration

Adverse events:
At every visit the CRF prompts the investigator to assess the patient for presence of infection as shown below.

NEW OR ONGOING INFECTION ASSESSMENT

Evaluate if a new infection has occurred since the last visit. If an infection has occurred, record on the adverse event page. Study drug should be withheld if the subject has a clinically significant infection.

On visits requiring a physical examination, the CRF also prompts the investigator to record new or worsening physical signs as an adverse event. However for most study visits the CRF has no prompt and does not document that the patient was assessed for treatment-emergent adverse events. The CRF contains an adverse event section after the in-treatment and post-treatment data for course 1 (pages 4-83 to 4-86) and for course 2 (pages 4-173 to 4-175). At the end of each treatment course the CRF asks if a patient experienced an adverse event during the study as shown below

ADVERSE EVENTS REPORT-Treatment Course 2

Did the subject experience any adverse events during the study? Y ☐ Yes N ☐ No

Is the event a new infection? Y ☐ Yes N ☐ No

Reviewers' comment:
The CRF was not optimally designed to capture treatment emergent adverse events. A check box at each visit would have been useful for confirming that the investigator had assessed the patient for adverse events.

Eligibility criteria for treatment course 2

The CRF indicates that the protocol allowed the use of antipsoriatic medications in the post-treatment period. This use is expected to influence the estimates of duration of response to first treatment and the assessment of response to retreatment.

Protocol No.:	Subject Initials	Subject No.:	
C99 - 711	☐☐☐	☐☐☐ - ☐☐☐	Visit 1B

ELIGIBILITY CRITERIA FOR TREATMENT COURSE 2

EXCLUSION CRITERIA

YES Y	NO N		*Treatment History*
☐	☐	11.	Subject has had treatment with another investigational drug or approved therapy for investigational use within 4 weeks prior to study drug administration.
☐	☐	12.	Subject has had treatment with systemic retinoids, systemic steroids, methotrexate, cyclosporine, azathioprine, or thioguanine within the 4 weeks prior to study drug administration.
☐	☐	13.	Subject has had treatment with high potency corticosteroids (Class I and II) within the 4 weeks prior to study drug administration.
☐	☐	14.	Subject has had treatment with moderate potency topical corticosteroids (Class III and IV) (other than on the scalp, palms, groin and/or soles) within the 2 weeks prior to study drug administration .
☐	☐	15.	Subject has had treatment with vitamin D analogues and topical retinoids (other than the scalp, palms, groin and/or soles) within 2 weeks prior to study drug administration.
☐	☐	16.	Subject has had treatment with keratolytics or coal tar (other than the scalp, palms, groin and/or soles) within 2 weeks prior to study drug administration.
☐	☐	17.	Subject has had phototherapy within 4 weeks prior to study drug administration.

QUESTIONS 11 - 17 MUST BE ANSWERED "NO" FOR THE SUBJECT TO BE ELIGIBLE FOR PARTICIPATION IN THE STUDY.

Past medical history

During the study a few patients developed variants of psoriasis or required non-allowed medications for control of psoriatic arthritis. Line listings were reviewed for all patients to look for evidence of these conditions at baseline or in past history. Very few patients had history of psoriasis variants. A notable number of patients had history of psoriatic arthritis.

The line listings confirm the presence of common chronic medical conditions in the study patients. For some patients few or no adverse events were captured during the study. The incidence of adverse events over the two treatment and follow up periods (a total time span of one year) is somewhat lower than might be expected based on waxing and waning or new manifestations of chronic diseases.

Primary Efficacy Outcomes

Response to first treatment course

The study met its primary endpoint, namely the proportion of patients with ≥75% improvement in PASI score from baseline to the end of the first treatment period (visit 13

A) was greater in the alefacept group. The absolute difference in the proportions was 11%.

Table 31 shows that response to treatment was not affected by the stratification variables of severity of psoriasis or history of previous major antipsoriatic therapy. Response was also not affected by age or gender. Response to treatment was numerically higher in non-Caucasians compared to Caucasians, however the number of non-Caucasians was small. This was not confirmed in study 712. With regard to geographic region, treatment response was numerically lower in region E (Southern); this trend was also seen in study 712.

Table 31. Responders by Strata, Geographic Region, Age, Gender, and Race

		Placebo (N=186)		7.5 mg (N=367)	
PASI > 20, No prior systemic therapy		0/ 8	0	3/ 18	(17)
PASI > 20, Prior systemic therapy		1/ 48	(2)	9/ 93	(10)
PASI <= 20, No prior systemic therapy		0/ 38	0	13/ 74	(18)
PASI <= 20, Prior systemic therapy		6/ 92	(6)	28/182	(15)
No prior systemic therapy		0/ 46	0	16/ 92	(17)
Prior systemic therapy		7/140	(5)	37/275	(14)
PASI > 20		1/ 56	(2)	12/111	(11)
PASI <= 20		6/130	(5)	41/256	(16)
GEOGRAPHIC REGION:	A	0/ 37	0	9/ 68	(13)
	B	3/ 39	(8)	14/ 79	(18)
	C	1/ 30	(3)	16/ 66	(24)
	D	1/ 41	(2)	9/ 90	(10)
	E	2/ 39	(5)	5/ 64	(8)
AGE:	<30	1/ 26	(4)	6/ 41	(15)
	30-39	2/ 42	(5)	14/ 90	(16)
	40-49	1/ 48	(2)	12/ 96	(12)
	50-59	3/ 41	(7)	14/ 90	(16)
	>59	0/ 29	0	7/ 50	(14)
GENDER:	Women	4/ 59	(7)	20/107	(19)
	Men	3/127	(2)	33/260	(13)
ETHNIC GROUP:	Non-caucasian	1/ 24	(4)	8/ 35	(23)
	Caucasian	6/162	(4)	45/332	(14)

Response to treatment was also examined by study center. Taking into consideration the small number of patients enrolled at each center, there was no evidence that responses to study treatments differed between centers.

Statistical analyses to identify baseline prognostic factors and potential interaction with treatment confirmed the observation of the summary data. Age, ethnic group, baseline CD4 and CD8 counts, and randomization stratum were not important predicators of response. The treatment responses were consistent across the strata of these factors. For this analysis the percentage change in PASI score at endpoint was used. There was no interaction between treatment and baseline CD4, or CD8 lymphocyte counts. The

adjusted difference in % reduction in PASI between drug and placebo groups was approximately 20% at endpoint (visit 13A).

Effect Of Body Weight on Treatment Response

Patients whose body weight at screening was 50 kg or more were to receive placebo or 7.5 mg alefacept. Patients whose body weight at screening was less than 50 kg were to receive placebo or 5.0 mg alefacept. The distribution of body weights and the relationship between body weight and response were explored. Only five patients (< 1% of total, all women) weighed < 50 kg. The mean body weight was 92 kg (median 91 kg LQ 77 and UQ 105).

Reviewers' comment
Even though the protocol stated that patients weighing less than 50 kg were to receive placebo or 5.0 mg of alefacept, the case report tabulation indicated that patients weighing <50 kg received 7.5 mg of alefacept.

When the sponsor was alerted to this inconsistency, the sponsor confirmed that patients weighing less than 50 kg actually did receive 5 mg of alefacept.

There was a suggestion that patients weighing > 85 kg (approximately 60% of total) had lower response rates compared to patients weighing < 85 kg. (**Table 32**). This trend of lower response rates in patients with higher body weight was also observed in the 10 mg IM dose group in study 712.

Table 32. Relationship between Body Weight and Response to Treatment in Course 1

	Placebo	**7.5 mg**
WEIGHT (kg)		
<50 kg	0	1/ 5 (20.0)
50-69 kg	1/ 18 (5.6)	10/ 51 (19.6)
70-84 kg	10/ 53 (19)	22/ 89 (24.7)
85-99 kg	3/ 53 (5.7)	9/ 96 (9.4)
100-114 kg	0/ 44	7/ 76 (9.2)
115+ kg	2/ 18 (11.1)	4/ 50 (8.0)

Reviewers' comment
There is insufficient information to recommend a specific dose for patients weighing <50 kg. There is a suggestion that patients with BW> 85 kg may be under-dosed.

The relationship between body weight and response was explored further by examining the relationship between % change in PASI score, change in CD4, and dose over lean body mass (LBM) in the alefacept-treated patients. Lower dose/LBM was associated with lower % reduction in PASI score. Even though this relation was statistically significant (not multiplicity adjusted), the R^2 for the regression fit was only 0.035. Therefore, only 3.5% of the variation in % reduction in PASI was contributed by dose/LBM. Lower body weight was associated with larger % reduction in PASI. However only 3.7% variation in % change in PASI is explained by body weight. Change in CD4 count was significantly related to % change in PASI. However, only 1.7% variation in % change in PASI was

contributed by the variation in change in CD4. Finally dose/LBM did not affect the change in CD4 count. Note that none of these associations were statistically significant for the placebo patients

STUDY OUTCOMES: SECONDARY EFFICACY

First Treatment Course: Secondary Outcomes

Various other secondary outcomes support to the primary efficacy outcome. They show similar, modest increases in the proportion of responders in the alefacept group compared to placebo (**Table 33**). By criterion of proportion of patients achieving clear to nearly clear skin by PGA, the absolute difference in response between placebo and alefacept groups was 7% in favor of alefacept. Using a less clinically meaningful outcome measure (proportion of patients with ≥50% improvement in PASI) the absolute difference in response between placebo and alefacept groups was 28% in favor of alefacept. The percentage decrease in PASI from baseline was 19±30% in the placebo group and 39±36 % in the alefacept groups.

Table 33. Efficacy Endpoints Based on Proportions Responding in the First Course

	Placebo	7.5 mg
PATIENTS DOSED IN FIRST COURSE	186 (100)	367 (100)
Primary Endpoint: PASI ≥75% Reduction from Baseline	7 (4)	53 (14)[a]
Secondary Endpoints:		
-PGA 'almost clear' or 'clear'	7 (4)	42 (11)
-PASI ≥50% Reduction from Baseline	18 (10)	138 (38)
-Target lesion induration of zero	15 (8)	78 (22)

(a) Comparison of treatments adjusted for geographic region and stratum P<0.001

Response to Second Treatment Course

Patients who received alefacept in the second course of study treatment showed a greater proportion of responses compared to patients who received placebo (**Table 34**). The absolute difference in proportions for the PASI-75 outcome was 15% using the pre-specified comparison between PASI at Visit 13 B (end of course 2) and PASI at Visit 1 A (baseline of course 1). Other secondary measures were also supportive. The percentage decrease in PASI (mean ± S.D.) from baseline was -31±32 in placebo and -50 ± 35 in the alefacept group. Eighteen patients in cohort 1 responded for the 1st course. Among these 18 patients, 12 (2/3) of them responded for the 2nd course. One hundred and thirty-six (136) cohort 1 patients did not respond to the 1st course but 24 (18%) of them responded to the 2nd course.